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Chalcone derivatives from pyrrole-2-aldehyde

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CHALCONE DERIVATIVES FROM PYRROLE-2-ALDEHYDE

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CHAPTER I

INTRODUCTION

Claisen[1] first synthesized Chalcone in 1881 by condensing acetophenone with benzaldehyde using sodium methoxide as condensing agent. Chalcone and its derivatives have been prepared primarily as intermediates for the synthesis of anthocyanins and other related pigments.

In recent years extensive preparation and study of chalcones has been carried out utilizing chalcones for their biological effects in medical and pharmaceutical fields. It has been shown that certain highly substituted compounds present in the flower pigments as additives to adhesive absorb ultraviolet radiation.[2] Carboxylic acid chalcones have become known for their therapeutic action in the treatment of chronic kidney diseases, diseases of the eye, and rheumatoid diseases, such as bursitis and osteoarthritis.[3] Treatment of chalcones with sulfuric acids to obtain γ-ketosulfones, used as chemotherapeutic agents, has been

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[1]L. Claisen, Berichte, XX (1887), 657.

[2]Henry Gilman and Louis F. Cason, "Some Addition Reactions of Chalcones. (I) The Preparation of Some γ-Ketosulfones," American Chemical Society Journal, LXXII (May, 1950), 3469-72.

[3]B. F. Hart, "Flavanone Compounds," U.S. 2 (February 23, 1960), 162, 926. Chemical Abstracts, LIV (1960), 12161.

under investigation and useful results have been obtained.[4] Many of these γ-ketosulfones are used to identify small amounts of sulfuric acid obtained from the cleavage and rearrangement of certain sulfones.[5] In the research on genetic factors which regulate the formation of flavonoidal factors in organisms, a suitable method for determining these compounds in small amounts in plant tissue is of very great importance and chalcones have been under investigation to serve this purpose.[6] The observation of insecticidal[7] bacteriostatic and tuberculostatic activities in chalcones has led to extensive investigation of chalcones.

A literature survey revealed that pyrrole has not been introduced to make α - β unsaturated ketones to produce chalcones or chalcone-type substances in analogy to benzal-acetophenone and its derivatives. Therefore, the purpose of

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[4]T. A. Geissman and David K. Fukushima, "Flavanones and Related Compounds. (V) The Oxidation of 2'-Hydroxy Chalcones with Alkaline Hydrogen Peroxide," American Chemical Society Journal, LXX, Part 2 (May, 1948), 1686-96.

[5]Gilman and Cason, loc. cit.

[6]T. A. Geissman and S. L. Friess, "Flavanones and Related Compounds. (VI) The Polarographic Reductions of Some Substituted Chalcones, Flavones and Flavanones," American Chemical Society Journal, LXXI, Part 3 (December, 1949), 3893-902.

[7]Patrick F. Devitt, Anita Timoney, and Michael A. Vickory, "Synthesis of Heterocyclic-Substituted Chromones and Chalcones," Journal of Organic Chemistry, XXVI (December, 1961), 4941-44; and Gilman and Cason, loc. cit.

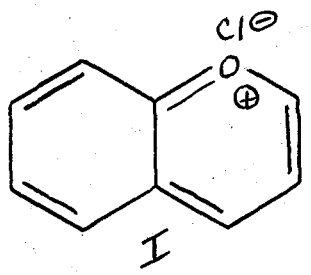
this work was to attempt condensation reactions of acetophenone with pyrrole-2-aldehyde to prepare chalcone derivatives. Ultimately it is hoped to test these compounds for possible biological activity.

CHAPTER II

CHALCONE RELATED PIGMENTS IN NATURE

The plant pigments can basically be classified into two groups; the plastids which constitute the protoplasmic structure of the plants, and the anthocyanins, responsible for the various shades of blue, red, violet, mauve, and magenta found in nature.

The anthocyanins are glycosides with the parent substance being the heterocyclic nucleus benzopyrylium chloride (I).[1]



I

The sugar-free pigments, or aglucons, are anthocyanidins[2] which are amphoteric. The acid salts of anthocyanidins are red, the metallic salts with bases blue, and the neutral pigments are purple. Anthocyanidins are soluble in water.

The flavones which occur in combination with rhamnose or glucose as glycosides and are associated with the tannins

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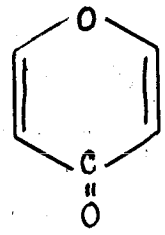
[1]K. W. Bentley, The Natural Pigments (New York: Interscience Publishers, 1960), IV, 1-51.

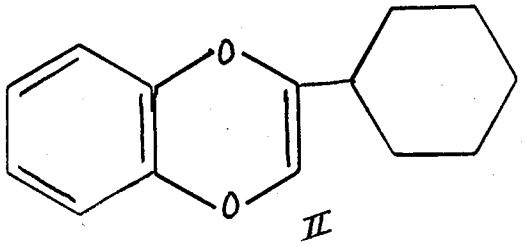
[2]Ibid.

are another important group of plant pigments. These flavones with alkalies develop a deep yellow color which signifies their presence. The basic unit of the flavones is γ-pyrone.



γ-pyrone

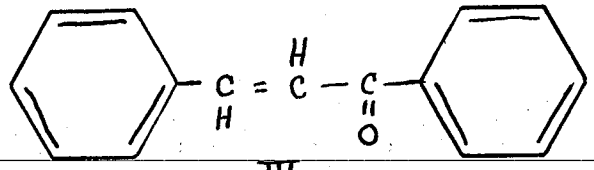
Flavone or 2-phenylbenzo-4-pyrone (II).



II

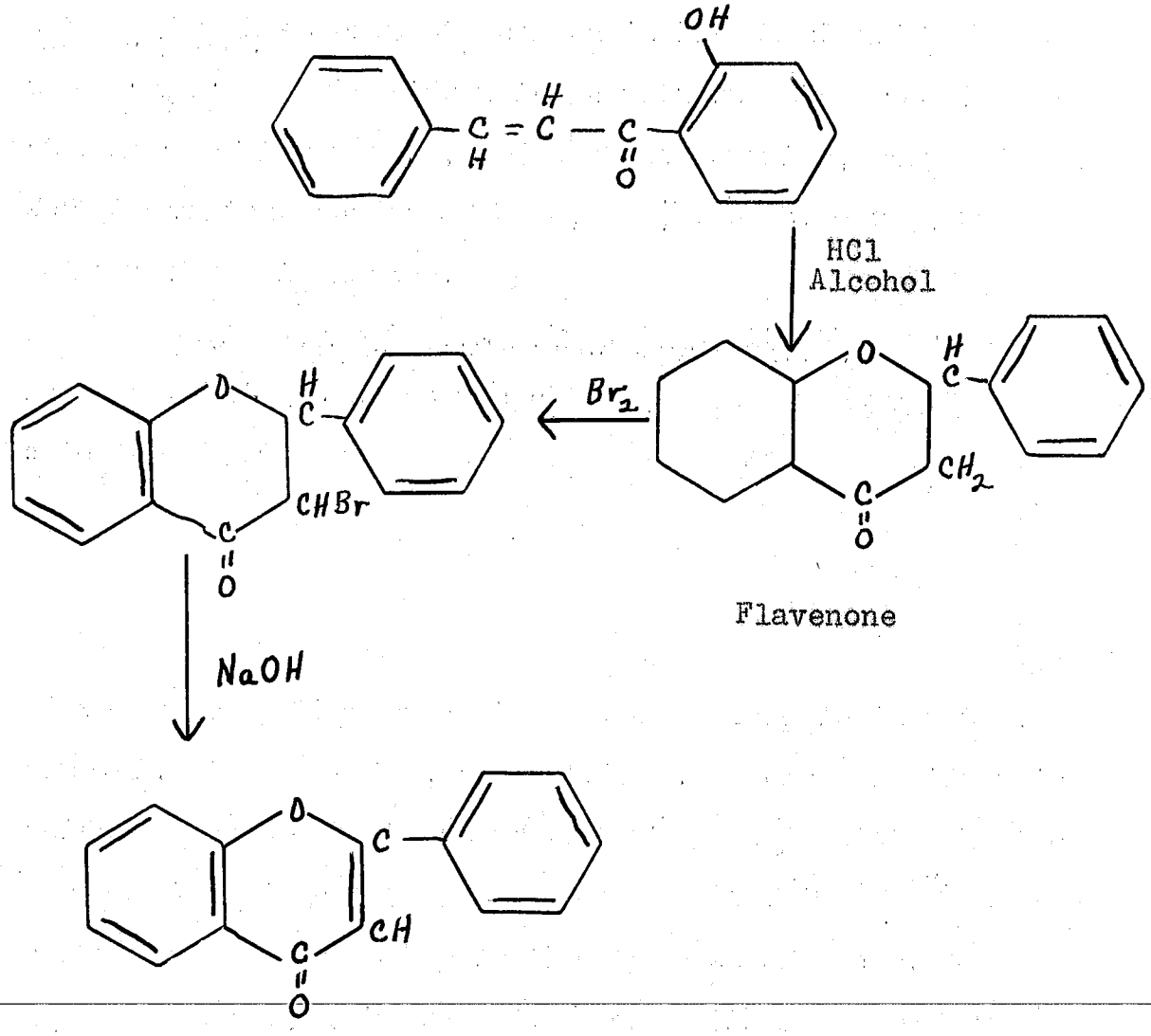
Flavones are yellow crystalline solids soluble in water, alcohol, mineral acids, and alkalies. Their solubility in acids is due to the basic nature of the oxygen atom in the pyrone ring, which can form oxomium salts. These salts are colored and are unstable in the presence of water.

Chalcone or benzalacetophenone (III) is the key compound linking these two groups of compounds.



III

The following two syntheses[3] illustrate the relationship between chalcone and flavone, and chalcone and anthocyanidins respectively.

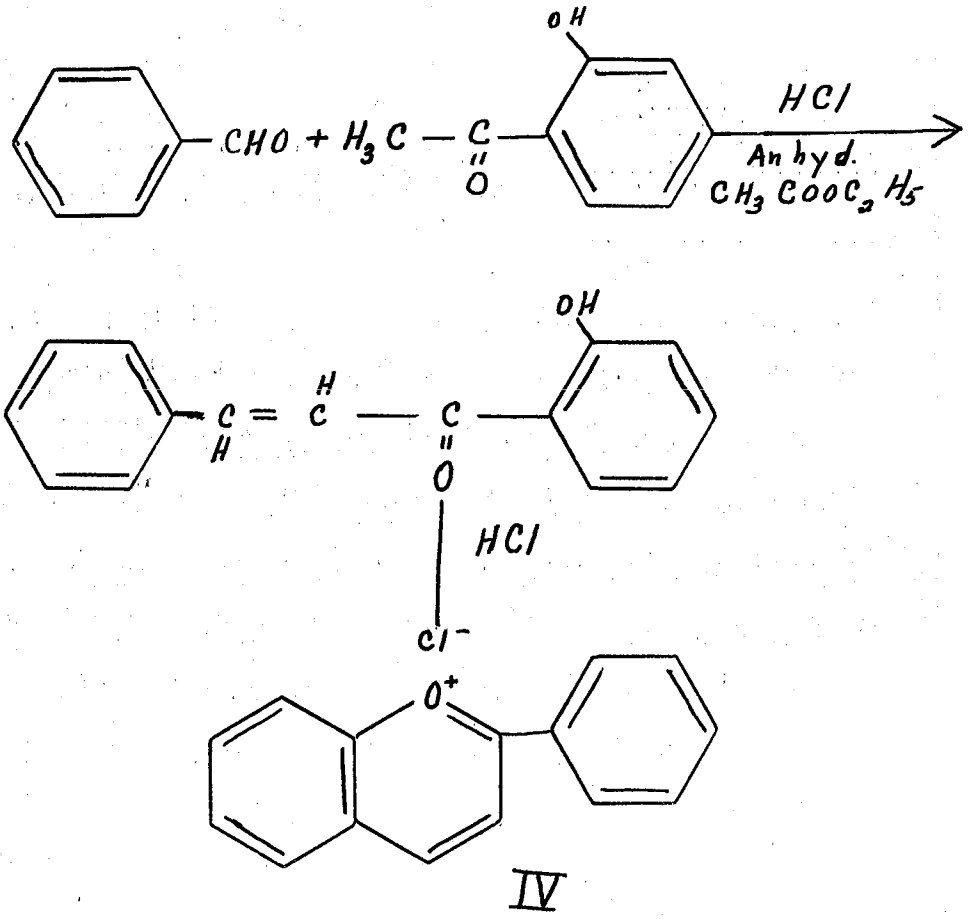


Flavenone

Flavone

and

[3] Ibid.



IV

Thus, the chalcone derivatives are intermediates for the synthesis of anthocyanins, pigments responsible for the colors found in the flowers of plants. The chalcone derivatives are also intermediates in lignin-like structures and in the synthesis of certain naturally occurring tanning substances. These pigments[4] are different from the plant pigments

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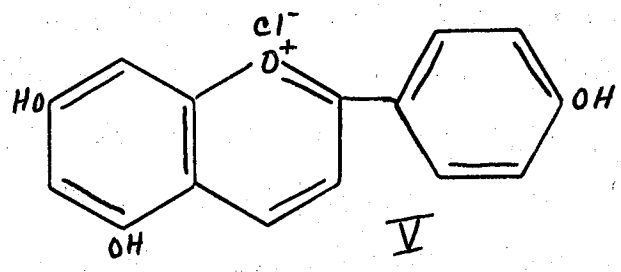
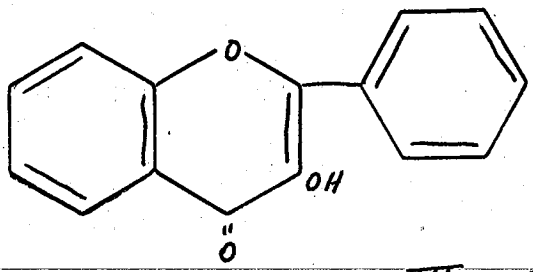
[4]R. A. Hendry, "Chalcones Derived from m-Nitroacetophenone" (unpublished Master's thesis, College of the Pacific, Stockton, California, 1952).

which include chlorophylls, carotenes, and xanthophylls found in the cytoplasm, while anthoxanthidins and anthocyanins are found in vacuolar[5] sap. The anthocyanins have from one to three sugar groups attached through hydroxyl groups, which are hydrolyzed from the pigment by treating with hydrochloric acid. Anthocyanidins are sugar-free anthocyanins. Anthocyanidins (V) are hydroxy[6] derivatives of the 2-phenylbenzopyrylium salt (IV).



V

The anthoxanthidins are the derivatives of flavone (II) and include flavones, flavanones, and flavonols (VI).



VI 3-hydroxy flavone.

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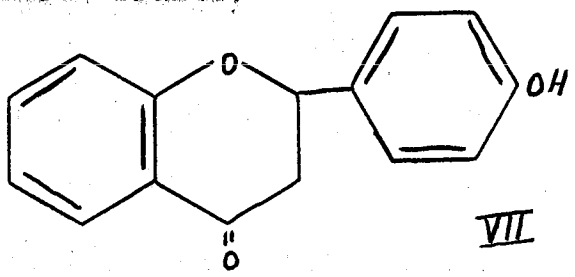
[5]Ibid.; and Lioyed J. Mitchell, "Condensation Reaction of TEREPHTH-Aldehyde and Acetophenone" (unpublished Master's thesis, College of the Pacific, Stockton, California, 1955).

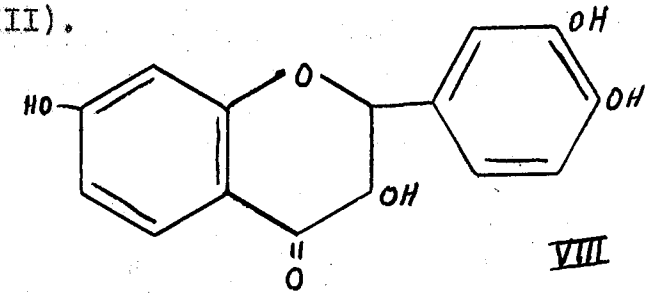
[6]Mitchell, Ibid.; and Bentley, loc. cit.

Naturally occurring anthocyanins have hydroxyl or methoxyl groups in the 3-, 5-, and 7- positions and various pigments result from substituted hydroxy and methoxy groups in the phenyl group. Flavanones, being the reduced form of flavones, are found in nature, such as naringenin (VII) in the peel of citrus fruits.



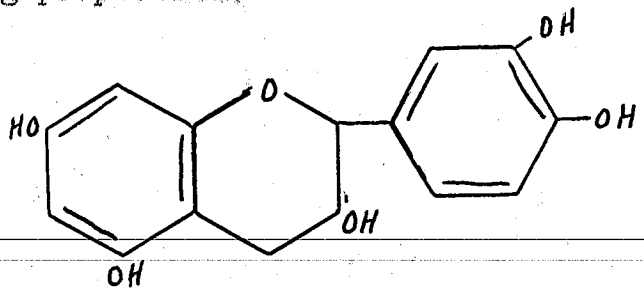
VII

Flavanols are the reduced form of flavonols such as fusitin(VIII).

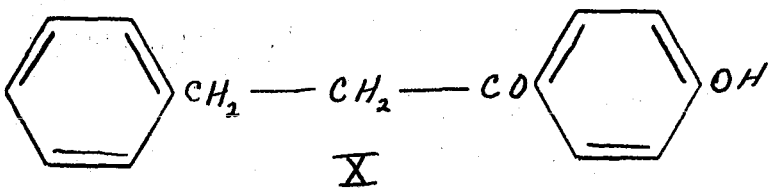


VIII

Isoflavones, which are very rare in nature, are different from flavones in that the phenyl group is in the 3- position rather than in the 2- position. The reduced form of anthocyanidins known as catechins, such as epicatechin (IX), have tanning properties.

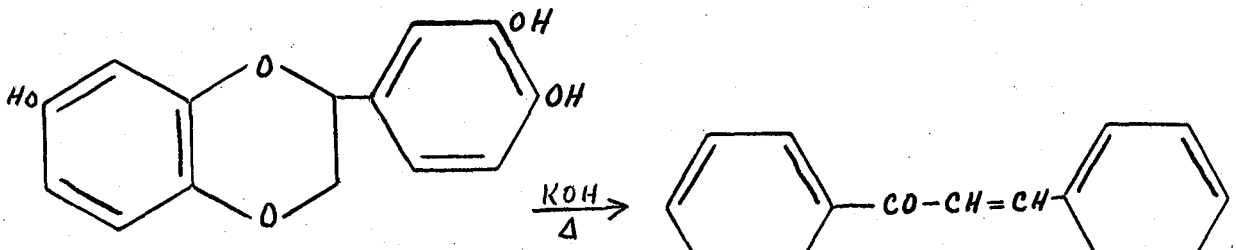


Another naturally occurring group of compounds related to the anthoxanthin pigments could best be represented by phloretin (X) which is the reduced form of the chalcone 2,4,4′-trihydroxybenzalacetophenone.



X

Butin, a naturally occurring flavanone, can be converted to the chalcone-butein, to show the close relationship between anthoxanthin pigments and the class of pigments of which phloretin is a member.



Butin Butein

Formation and cyclization[7] of a polymeric chalcone (XI) into a polymeric form of a flavanone (XII) takes place in the Fries rearrangement of the monoacetate of vanallin (XIII) and gives a product with properties similar to those of lignin.

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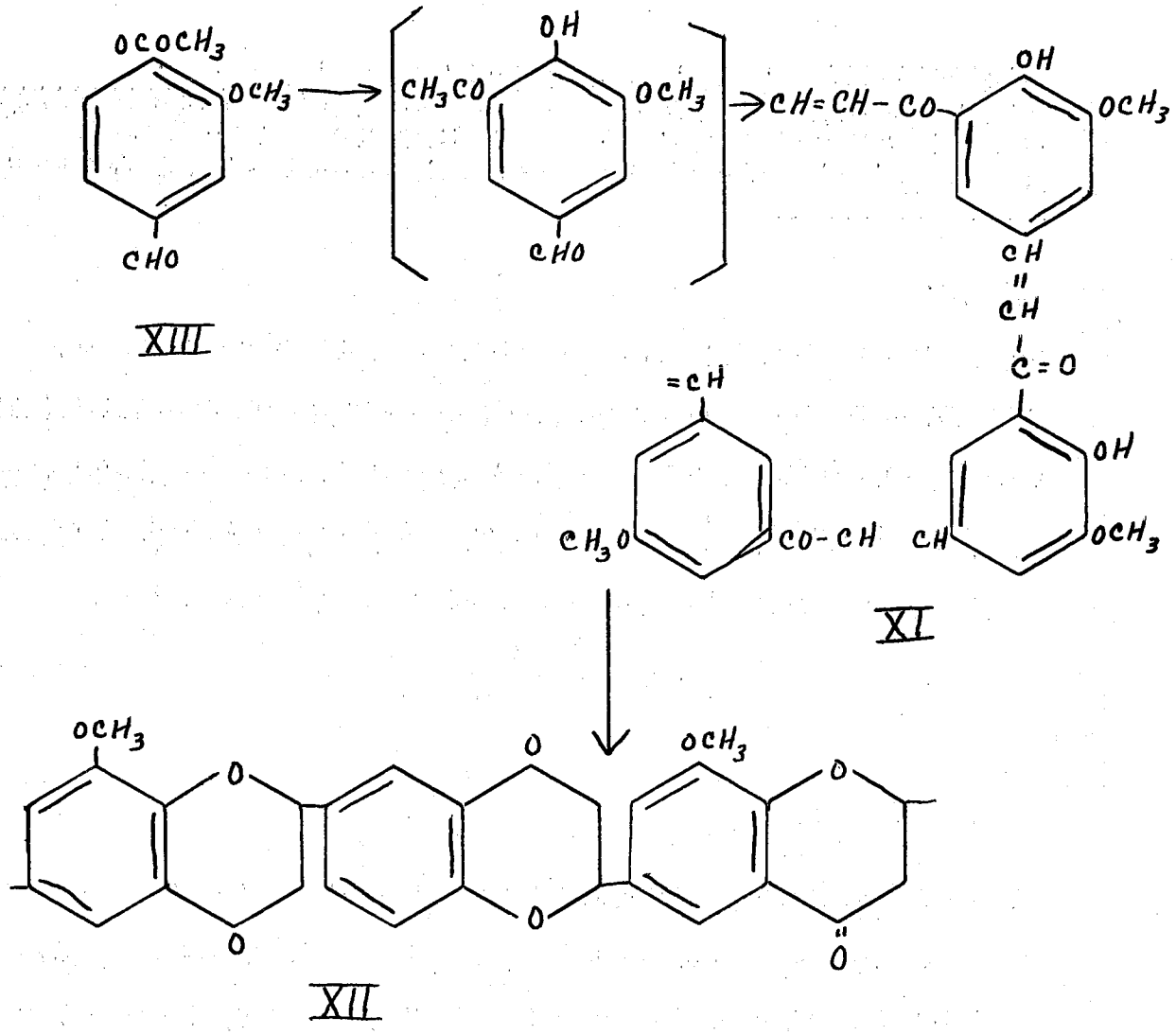
[7]T. A. Geissman and David K. Fukushima, "Flavanones and Related Compounds. (V) The Oxidation of 2′-Hydroxy Chalcones with Alkaline Hydrogen Peroxide," American Chemical Society Journal, LXX, Part 2 (May, 1948), 1686-96.



XIII

XI

XII

Tannins, and the compounds which are used as tanning agents in the leather industry, occur in nature often with flavones. Treatment[8] of certain hydroxy-chalcones with hydrochloric acid-alcohol and zinc-dust form pinacols. If chalcones with 3- and 4-hydroxy groups and a 2'-hydroxy

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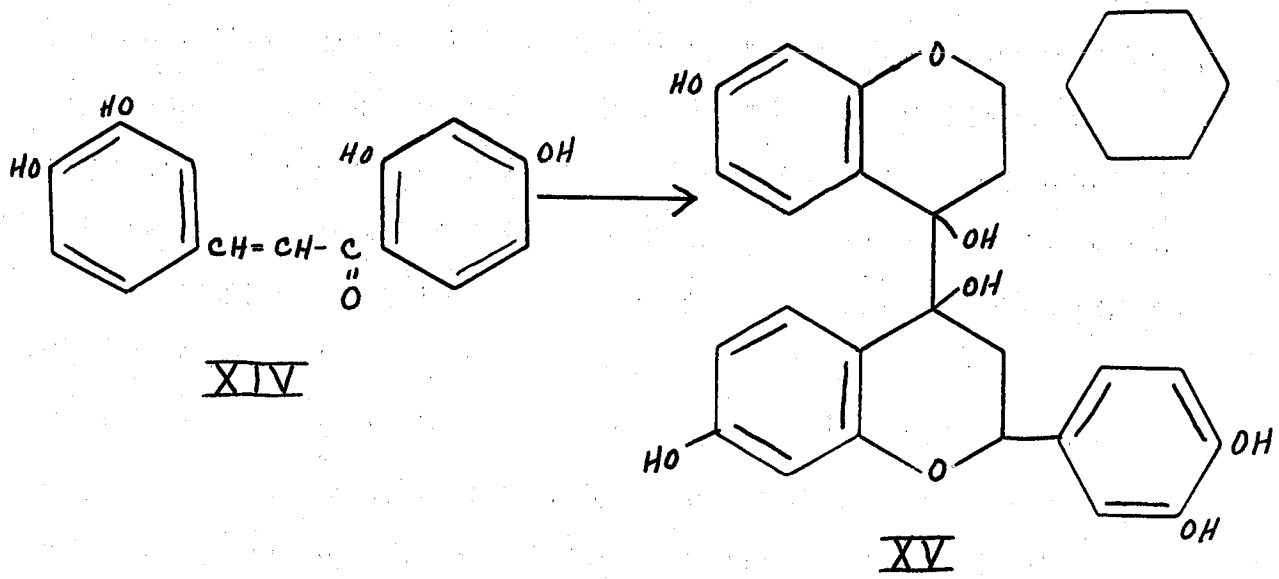
[8]Hendry, loc. cit.

group--a flavone--are reduced by the above method they form pinacols of almost the same properties as those of naturally occurring phlobatannins.

Reduction[9] of tetra- (XIV) and penta-hydroxy chalcones produces the pinacols (XV)[10] with properties of quebracho and hemlock tannin respectively.



XIV XV

One class of pigments could be converted into another by various chemical reactions. Quercetin,[11] a flavonol, can be converted into a cyanidin--an anthocyanidin--and then into epicatechin by a series of reactions. Chalcones play an important role as intermediates in the synthesis of all these

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[9]H. Gilman, Organic Chemistry (New York: Wiley and Sons, 1938), Vol. II.

[10]Bentley, loc. cit.

[11]Gilman, loc. cit.

compounds and the correlation[12] between oxidases in the flowers of plants and the amounts of anthoxyanins present in them can account for the fact that in the biological synthesis of almost all these naturally occurring compounds chalcones are temporary intermediates.

Leuco-anthocyanidins[13] of glycosidic properties, white and amorphous, occur either along with anthocyanidins or its precursors from a common source.

Anthocyanidins,[14] flavones, and all other naturally occurring pigments are formed from a basic C_6-C_3-C_6 structure. This structure can be from hexoses and smaller sugar units. The sugars can cyclize to phenolic type aromatic structures and then two of these C_6 structures join through a type of aldol condensation with a triose. By isolation of the various products as precursors of the anthocyanidins the validity of the theory could be confirmed.

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[12] R. A. Gortner and W. A. Gortner, Outlines of Biochemistry (New York: Wiley and Sons, 1949).

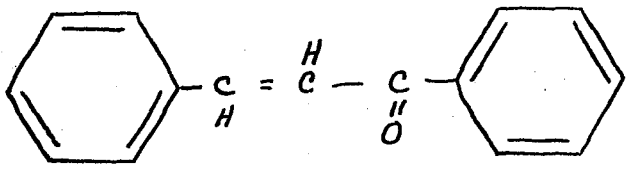
[13] Bentley, loc. cit.

[14] Ibid.

CHAPTER III

CHALCONES

Chalcone is an α, β -unsaturated ketone which is also known as benzylideneacetophenone, phenyl-styrl-ketone, or most commonly, a benzalacetophenone.



Chalcone as a yellow, crystalline compound is the name given to the parent compound of a large number of substituted derivatives known as chalcones. Claisen prepared chalcone in 1881[1] by condensation of acetophenone and benzaldehyde. Various agents have been used as condensing agents, but basically a suitable acid or base are the usual agents. The most common condensing agents which have been used are sodium hydroxide,[2] sodium methoxide,[3] anhydrous hydrogen

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[1] L. Claisen, Berichte, XX (1887), 657.

[2] K. W. Bentley, The Natural Pigments (New York: Interscience Publishers, 1960), IV, 1-51; E. P. Kohler and H. M. Chadwell, Organic Synthesis (New York: Wiley and Sons, 1922), Vol. II; and T. A. Geissman and David K. Fukushima, "Flavanones and Related Compounds. (V) The Oxidation of 2-Hydroxy Chalcones with Alkaline Hydrogen Peroxide," American Chemical Society Journal, LXX, Part 2 (May, 1948), 1686-96.

[3] Claisen, loc. cit.

chloride,[4] boron trifluoride,[5] and aluminum chloride.[6]

Condensation[7] of an ortho-hydroxy acetophenone and benzaldehyde yields a chalcone, which on treatment with ten per cent sulfuric acid gives a flavanone. Treating the flavanone with bromine and the subsequent treatment of the resulting bromo addition compound with sodium hydroxide affords a flavone. If the flavanone is treated with amyl-nitrite and hydrochloric acid in an alcoholic solution, it yields an oximino substance which upon treatment with ten per cent sulfuric acid yields a 3-hydroxy flavone--a flavonol.

Anthocyanidins are obtained by treating the ortho-hydroxy chalcones (obtained from the condensation of ortho-hydroxy benzaldehyde and acetophenone) with hydrochloric acid.

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[4]Bentley, loc. cit.

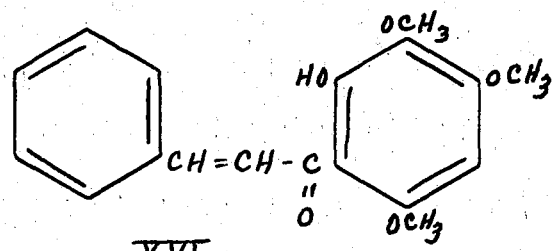
[5]Lioyed J. Mitchell, "Condensation Reaction of TEREPHTH--Aldehyde and Acetophenone" (unpublished Master's thesis, College of the Pacific, Stockton, California, 1955).

[6]N. O. Callaway and Louis D. Green, "Reactions in the Presence of Metallic Halides. (I) β-Unsaturated Ketone Formation as a Side Reaction in Friedel-Crafts Acylations," American Chemical Society Journal, LIX (1937), 809-11.

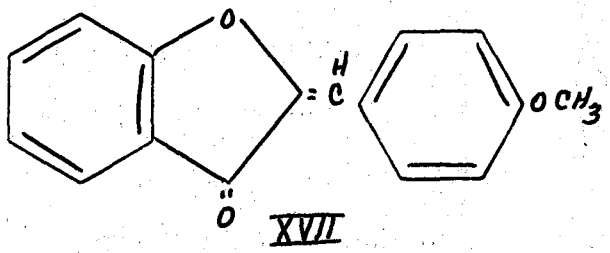
[7]H. Gilman, Organic Chemistry (New York: Wiley and Sons, 1938), Vol. II.

Oxidation of 2′-hydroxy[8] chalcones--if not substituted in the 6′-position--yield 3-hydroxy-flavones; but, if the 2′-hydroxychalcones are substituted with a methoxy group in the 6′-position, oxidation yields a benzalcoumaranone and a small amount of a flavonol.

For example, 2′-hydroxy-3′, 4′, 6′-trimethoxy chalcone (XVI) gives mostly 4′, 4, 6-trimethoxy benzal-coumaranone (XVII).



XVI



XVII

Certain chalcones can be oxidized to epoxy[9] derivatives by hydrogen peroxide in an alkaline medium, and then converted to a disubstituted glycolic acid by treatment with alkali. The oxidation of the resulting glycolic acid with lead tetra-acetate yields a ketone of the desoxybenzoin type, a class of compounds which are useful intermediates in the preparation of a number of physiologically active agents. An example of the physiologically active agents prepared by

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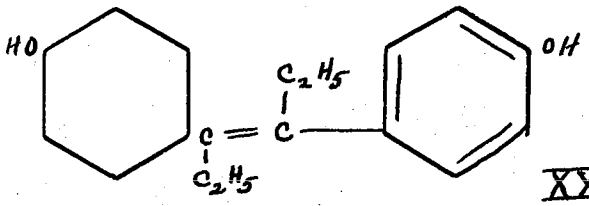
[8]Geissman and Fukushima, loc. cit.

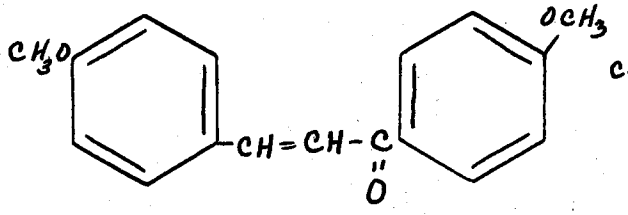
[9]E. Weitz and A. Scheffer, Ber., LIV, Part B (1921), 2327-44; and R. A. Hendry, "Chalcones Derived from m-Nitro-acetophenone" (unpublished Master's thesis, College of the Pacific, Stockton, California, 1952).

means of chalcones is diethylstilbestrol (XXII), a drug whose estrogenic properties are greater than those of estrone, one of the natural occurring female hormones.

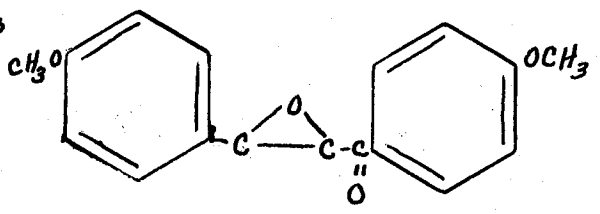


XXII

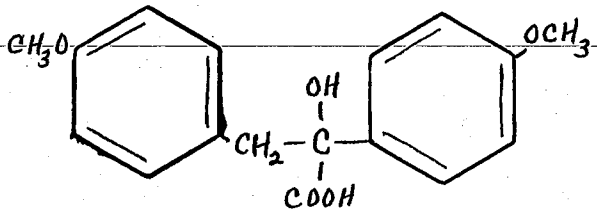
Diethylstilbestrol is synthesized as follows:[10] 4,4'-dimethoxy chalcone (XVIII) is converted to an epoxy derivative (XIX), then to a disubstituted glycolic acid (XX), and finally to desoxy-anisoin (XXI), which is the intermediate for the synthesis of diethylstilbestrol.



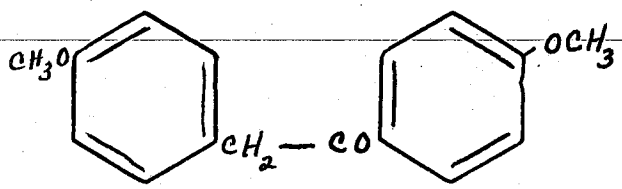
XVIII



XIX



XX



XXI

[10] Hendry, ibid.

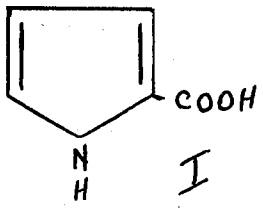
Disubstituted glycolic acids have also been used as intermediates for synthesis of mydriatics, by preparing basic esters of the acids by condensing the glycolic acid with 2-(1-piperidyl)-ethyl alcohol.

CHAPTER IV

SELECTION OF EXPERIMENTAL FACTORS GOVERNING 1) PYRROLE-2-ALDEHYDE AND 2) ACETOPHENONE DERIVATIVES

I. PYRROLE-2-ALDEHYDE

Soon after Runge discovered pyrrole in 1834 by the distillation of coal tar, bone oil, and other products,[1] pyrrole became of great interest as it was found in many compounds widely distributed in nature. By 1880 it had been recognized in the indigo, in blood, and chlorophyll. Two amino acids derived from pyrrole, proline (I) and 4-hydroxy-proline (II), are constituents of many proteins.



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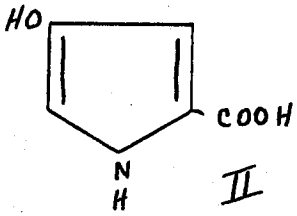

II

Another important pyrrole derivative is porphobilinogen (III) which is excreted in human urine under certain pathological conditions.

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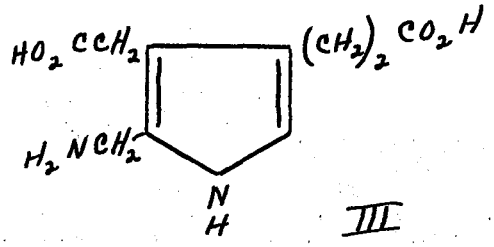
[1]Henry Gilman and Louis F. Cason, "Some Addition Reactions of Chalcones. (I) The Preparation of Some γ-Ketosulfones," American Chemical Society Journal, LXXII (May, 1950), 3469-72.



III

The presence of one nitro group, or a carbonyl group, permits electrophilic substitution under conditions usual to benzene and stabilizes the ring to acids.[2] No simple free 2- or 3-hydroxy pyrrole has been prepared; reactions which could lead to these compounds give the tautomeric carbonyl derivatives or their decomposition products. Many alkylpyrroles have been synthesized in connection with work on the porphyrin pigments and the Wolff-Kishner reduction of acylpyrroles obtained by Knorr's synthesis is a common method.

Pyrrole ketones could be obtained by a modification of Knorr's synethsis or by acylating a pyrrole directly with acetic anhydride. Pyrrole ketones are stable and undergo standard reactions.

Pyrrole-2-aldehyde does not undergo either cannizzaro or benzoin reactions due to resonance stabilization of the aldehyde:

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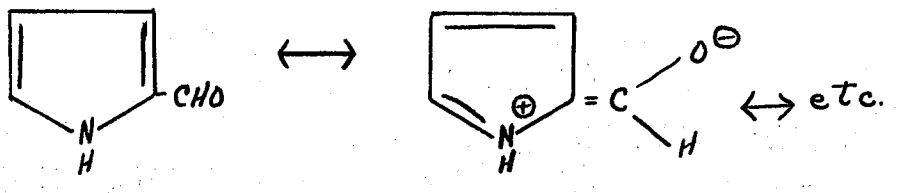
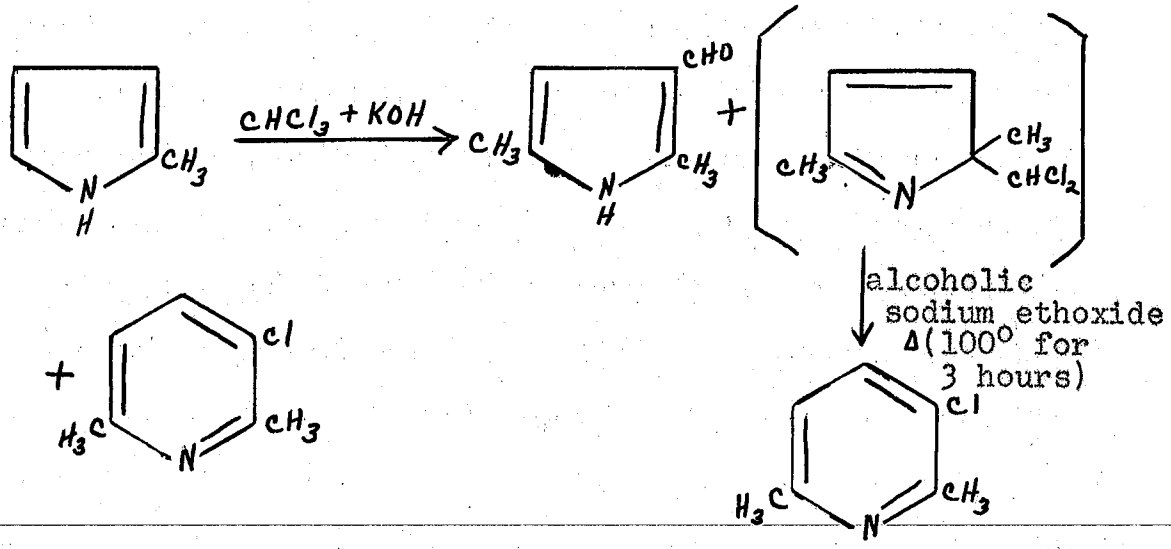
[2]Alsoph H. Corwin, The Chemistry of Pyrrole and its Derivatives (Heterocyclic Compounds, ed. Robert C. Elderfield, New York: Wiley and Sons, 1950), pp. 277-342.



The first method for preparation of a pyrrole-aldehyde utilizing the Reimer-Tiemann[3] reaction gave a very low yield ∝-aldehyde due to side reactions. Using the aldehyde prepared from 2,5-dimethyl-pyrrole, the reaction leads to 2-5-dimethyl pyrrole-3-aldehyde, 2,6-dimethyl-3-chloropyridine, and pyrrolenine derivatives.



The Gatterman synthesis of pyrrole-aldehyde proceeds in good yield when reactive phenols and phenol ethers are employed.

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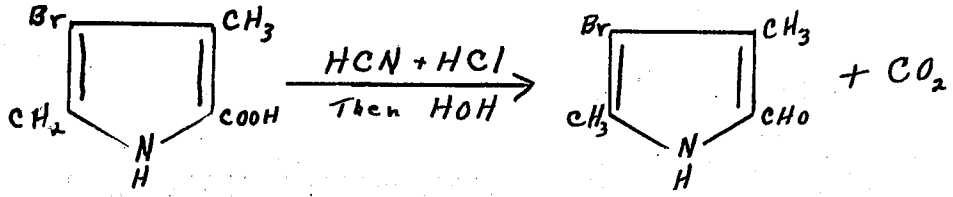
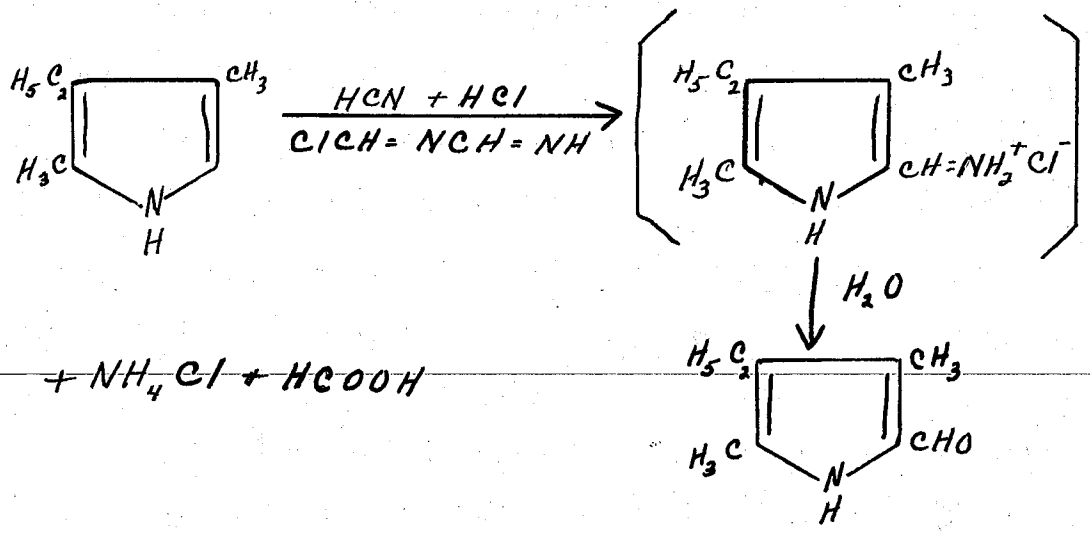
[3] Ibid.



Fisher and Zerweck introduced a new synthesis by which the formyl group is placed in either α- or β-position. During the reaction the chloromethyleneformamidine (NH=CH-N=CHCl) is produced which reacts with pyrrole and forms an aldimine hydrochloride. This is isolated before hydrolysis so it does not condense with any unsaturated pyrrole to form a dipyrrylmethane. An example of the method is the formation of kryptopyrrole aldehyde.[4]



[4]K. W. Bentley, The Natural Pigments, (New York: Interscience Publishers, 1960), IV, 1-51.

A modification of Fisher's[5] method using anhydrous zinc cyanide instead of anhydrous hydrogen cyanide has lead to a better yield[6] and is a safer procedure.

The best method of preparing pyrrole-2-aldehyde is accomplished by refluxing pyrrole with phosphorus oxychloride and dimethylformamide. The products, which can be isolated, are refluxed in aqueous sodium acetate.[7] Silverstein's method, giving yields of 90% compared to all other methods having yields not greater than 60%, is used in the present work and is described further in the preparation of the intermediates.

II. ACETOPHENONE DERIVATIVES

Phenyl esters are prepared by heating the phenol with acid chloride. The temperature at which Fries reaction is carried out depends upon whether an ortho- or para-hydroxy

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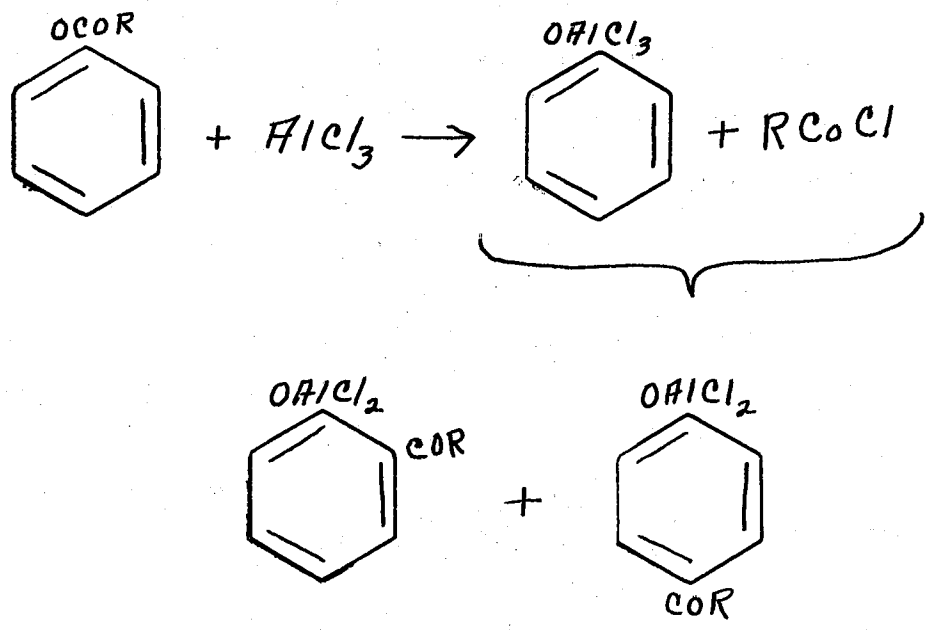
[5]Alsoph H. Corwin and John S. Andrews, "Studies in the Pyrrole Series. (II) The Mechanism of the Aldehyde Synthesis of Dipyrrylmethenes," American Chemical Society Journal, LVIII, Part 2 (1936), 1086-90.

[6]Roger Adams and I. Levine, "Simplification of the Gatterman Synthesis of Hydroxy Aldehydes," American Chemical Society Journal, XLV, Part 2 (1923), 2373-77; and Roger Adams and Edna Montgomery, "Simplification of the Gatterman Synthesis of Aromatic Aldehydes, II," American Chemical Society Journal, XLVI, Part 2 (1924), 1518-21.

[7]Robert M. Silverstein, Edward E. Ryskiewicz, and Saul W. Chaikin, "2-Pyrrolealdehyde, 3-hydroxymethylindole and 2-Hydroxymethylpyrrole," American Chemical Society Journal, LXXVI (September, 1954), 4485-86.

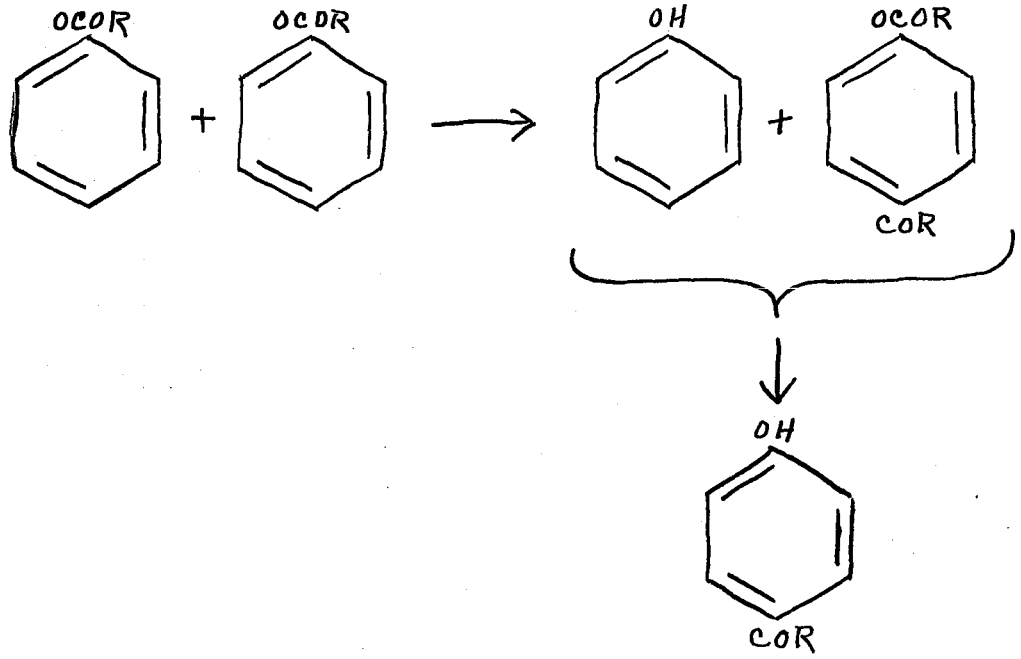
ketone is being prepared and upon reactivity of acyl group. If mild experimental conditions are required, a solvent, usually nitrobenzene, is used and no solvent if more severe conditions are necessary. The reaction takes place under one of the three proposed mechanisms:[8]

a) Ester reacts with aluminum chloride to yield acid-chloride and a phenoxy aluminum chloride which upon combination give a derivative of the hydroxy-ketone.



[8]K. W. Rosenmund and W. Schnurr, "Annalen der Chemie," Ann. 460 (1928), 56-98. Chemical Abstracts, Vol. 22 (May-September, 1928), 1579.

b) One molecule of phenyl ester is acylated by another molecule.



c) Acyl group shifts directly from oxygen atom to the carbon atom of the ring. The product is ortho-hydroxy or para-hydroxy ketone or a mixture of ortho- and para-, depending on temperature, solvent, and amount of aluminum chloride ($AlCl_3$). By varying these factors, the reaction could be led to produce either isomer in major yield. At 25° only para-hydroxy ketone (80% yield) can be obtained from methoa-crecyl acetate and $AlCl_3$, but at 165° only ortho-hydroxy ketone (95% yield) is the product. The presence of nitro benzene as a solvent lowers the temperature. $AlCl_3$ and phenyl ester are used in equimolar quantities. The increase in the size of acyl group of ester increases

formation of ortho-hydroxy ketone. The presence of a meta-directing group on the aromatic portion of phenyl ester interferes with Fries reaction; for example, reaction does not occur if there is a nitro group in ortho- or para-position. If phenyl ester contains a single alkyl group in phenolic ring, the position of this substituent has a great influence on the nature of the product; for example, esters of ortho-cresol yield predominantly para-hydroxy ketones, and those of meta-cresol yield ortho-hydroxy and esters of para-cresol only ortho-hydroxy ketones. Thus, an increase in the size of acyl group of the ester increases formation of ortho-hydroxy ketone; however, the significance of the acyl radical in determining the course of the rearrangement depends on the structure of the phenolic residue.

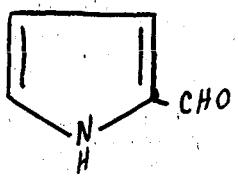
Structure of the phenolic portion of ester is an important factor in determining whether a Fries reaction takes place and whether ortho- or para-derivative is the principal product. If the phenolic residue carries a nitro or benzoyl group in either ortho- or para-position, the reaction does not take place. The presence of acetyl or carboxyl group in ortho- position hinders the reaction and in the para- position prevents it.

CHAPTER V

EXPERIMENTAL

I. PREPARATION OF THE INTERMEDIATES

Pyrrole-2-aldehyde



I

This aldehyde was prepared according to R. Silverstein's[1] improved method, a modified version of Shabica's method.[2]

Dimethyl formamide (14.6 g.) were placed in a one liter 3-neck reaction flask fitted with a mechanical stirrer, reflux condenser, drying tube, and a thermometer. The flask was immersed in an ice bath and 35.6 grams of phosphorus oxychloride was added during a period of about five minutes. The ice-bath was removed and the mixture stirred for an additional fifteen minutes. The ice-bath was replaced and 150 ml. of ethylene dichloride was added to the mixture.

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[1]Robert M. Silverstein, Edward E. Ryskiewicz, and Saul W. Chaikin, "2-Pyrrolealdehyde, 3-Hydroxymethylindole and 2-Hydroxymethylpyrrole," American Chemical Society Journal, LXXVI (September, 1954), 4485-86.

[2]A. Shabica, E. E. Howe, J. B. Ziegler, and M. Tishler, "Improved Synthesis of Indole-3-Aldehyde," American Chemical Society Journal, LXVIII, Part 1 (1946), 1156-57.

The mixture was cooled to 5° and 6.9 grams of pyrrole was added in small fractions sufficient to maintain the temperature below 10°c. The ice bath was removed and forty grams of powdered calcium carbonate was added carefully so as not to cause a rapid rise in temperature. At about 30-40° a strong reaction with evolution of hydrogen chloride took place. When this reaction subsided, the mixture was refluxed for thirty minutes and then cooled to room temperature. While maintaining this temperature, a solution of 150 grams of sodium-acetate in 200 ml. of water was added, the ice bath removed, and the reflux condenser was replaced with a take-off condenser. The mixture was distilled (80-85°) to remove the ethylene dichloride. The hot solution was filtered with the use of a Beuchner filter and the filtrate and precipitate were extracted with ether. The ether solution was washed with a 20% sodium-carbonate and evaporated by means of a rotating evaporator. The residue was then dissolved in hot petroleum ether, norite was added and filtered while still hot. Crystallization at room temperature gave long, thin white crystals of m.p. 40-43. The yield was 8.5 grams.

The literature reports a m.p. of 43-46° and yields of 49-90%. The yield of this aldehyde does not correspond to the yield cited. In subsequent preparations, this aldehyde was obtained in varying yields. The infra-red spectra is

in accordance with pyrrole-2-aldehyde but the melting points do not agree well with those of the literature. From one preparation, resulting crystals were obtained having a melting point of greater than 320°. The solid is most likely a salt of the pyrrole.

All these observations point to the fact that either more detailed procedures of the reported methods are required, or the necessary improvements are needed to establish a standard and proven method for preparation of pyrrole-2-aldehyde. Reported yields of 49-89% and continuous improvements of Silverstein's method by him and others[3] substantiate this fact.

For condensation of pyrrole-2-aldehyde with acetophenone and its derivatives, the final samples were prepared using a pyrrole-2-aldehyde sample purchased from Aldrich Chemical Company, Wisconsin. Phosphorus oxychloride, ethylene dichloride and pyrrole were obtained from Eastman Kodak. All other starting compounds used for this work were available in the Chemistry Department.

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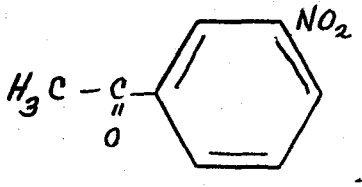
[3] Ibid.; and Robert M. Silverstein, E. E. Ryskiewiez, C. Willard, and Ruth C. Koehler, "Improved Synthesis of 2-Pyrrolealdehyde and of N-Methyl-2-Pyrrolealdehyde. Further Studies of Pyrrole Alcohols," Journal of Organic Chemistry, XX, Part 1 (1955), 668-71.

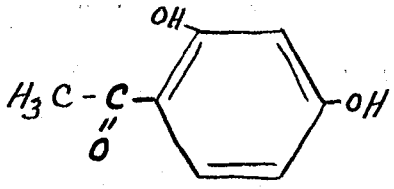
Meta-nitroacetophenone[4]



II

Acetophenone (12 g.) cooled to 0° was added to 60 cc. of cold concentrated NH_2SO_4 in five minutes while the mixture was kept below 15° and stirred continually. A mixture of 12 cc. concentrated H_2SO_4 and 9 cc. of fuming HNO_3 (ice cold) was added to above mixture which was at a temperature below -20°. It was cooled to this temperature by addition of more ice and salt. The mixture was stirred for an additional fifteen minutes and 120 cc. of ice and water were added. The solid was filtered and washed with ice-cold alcohol, then washed with cold water until filtrate was neutral to litmus paper. The solid was recrystallized from alcohol, m.p. 79-80°, yield 11 grams (65%). About 500 mls. of water was used for washings.

Preparation of resacetophenone (2-4-dihydroxy acetophenone)



III

[4]Charles Barkenlus and J. P. Clements, "The Nitration of ~~o~~-Chloro and ~~o~~-Bromo Acetophenone," American Chemical Society Journal, LVI (June, 1934), 1369-70.

For preparation of the dihydroxy derivative, the known method reported by R. Adams was followed.[5]

Anhydrous zinc chloride (33.0 g.) was dissolved in 31.6 mls. of glacial acetic acid by heating the mixture to 125°c. (temperature of the mixture is reported at 140°). To this mixture was added 22.0 grams of resorsinol while the mixture was stirred continuously. The solution was then heated on a sand bath until it began to boil at 135°c. (reported 152°). The heating was continued up to 148°, the solution was removed from the flame and allowed to sit for one-half hour. To this deep red-colored solution was added 100 ml. of 18% hydrochloric acid, the solution was mixed thoroughly, and the reaction flask put in an ice-bath to cool to 5°. After one-half hour, the mixture was filtered and the precipitate collected on a filter paper. The precipitate was then washed free of zinc salts with 200 ml. of hydrochloric acid (1:3) in 40 ml. portions. This deep orange product was air-dried at room temperature for a period of four days to a free-flowing state. It was then distilled at the reduced pressure of 10 mm. (boils at 180°). The light yellow distillate was allowed to sit overnight and dissolved in 360 mls. of hot diluted hydrochloric acid (1:11). The

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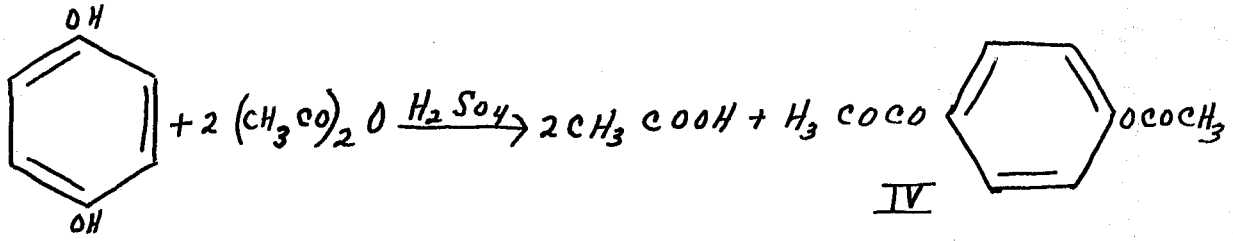
[5]S. R. Cooper, Resacetophenone (Vol. XXI of Organic Synthesis, ed. N. L. Drake. New York: Wiley and Sons, 1941), 103-04.

hot solution was filtered and cooled to 5° on ice-bath to form a reddish crystal. Further washings of the crystals with ice-water yielded 18 g. (60%) of a deep tan colored compound, m.p. 141-143° (reported 142-144 m.p. and 61-65% yield).

Preparation of Hydroquinone diacetate[6]



IV

To a mixture of 33 g. of hydroquinone and 57.1 ml. of acetic anhydride in a one liter Erlenmeyer flask, one drop of conc. sulfuric acid was added and the mixture stirred by hand gently. It warmed up very rapidly and the hydroquinone was dissolved. After five minutes, the clear solution was poured onto 240 mls. of crushed ice. A white crystalline solid was formed, which was collected on a filter and washed with 300 mls. of cold water. The solid crystals were dried to constant weight in desiccator over phosphorous pentoxide overnight. M.p. was 121-124°. (Reported yield, 55.8-57 g., 96-98%).

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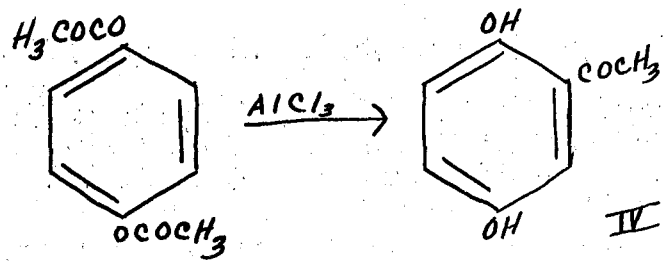
[6]W. W. Prichard, Hydroquinone Diacetate (Vol. XXVIII of Organic Synthesis, ed. H. R. Snyder. New York: Wiley and Sons, 1948), 68-69.

Preparation of 2-5-Dihydroxy Acetophenone[7]



IV

A mixture of 5 grams of dry hydroquinone diacetate (IV) and 11.6 grams of anhydrous aluminum chloride were ground into a fine powder in a mortar and introduced into a dry 200 mls. round bottomed flask which was fitted with air condenser and a calcium chloride tube connected to a gas-absorption trap.

The flask was placed in glycerine bath and heated slowly so that in one-half hour, hydrogen chloride evolution began at 100°c. temperature (reported 110-120°). The temperature was then raised slowly to 160-165° and maintained at this temperature for about three hours. After about two hours the evolution of hydrogen chloride became extremely slow and the mixture was a green paste. The flask was then removed and the mixture cooled to room temperature.

In order to decompose the excess aluminum chloride, about 35 grams of crushed ice were added to the mixture, followed by 2.5 ml. of concentrated hydrochloric acid. The

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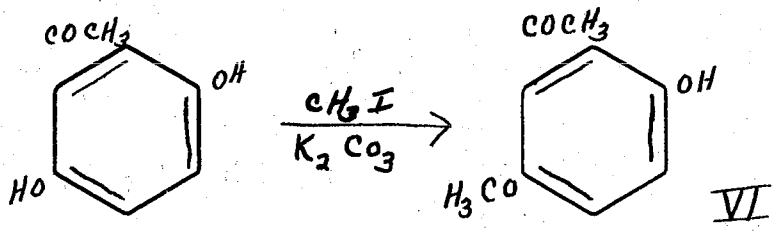
[7]N. M. Shah, 2,5-Dihydroxy Acetophenone (Vol. XXVIII of Organic Synthesis, ed. H. R. Snyder. New York: Wiley and Sons, 1948), 42-43.

solid thus obtained was collected on a filter paper and washed twice with 10 mls. of cold water. Green silky needles were obtained (3.5 g.). M.p. 202-203°.

Preparation of 2-Hydroxy-5-Methoxy Acetophenone[8] (Quinacetophenone Monomethyl Ether)



VI

Dry quinacetophenone (V)(3.0 g.) which had been dried for three hours at 110° was placed in a 200 ml. round bottomed flask fitted with a reflux condenser and a calcium chloride tube. After the addition of 30 mls. of dry acetone, the mixture was warmed on a steam bath to dissolve the dihydroxy and the resulting green solution was cooled to room temperature under tap water. To this solution was added 2.8 grams of anhydrous potassium carbonate followed by 4.2 grams of methyliodide. The mixture was then refluxed on a water bath for six hours at temperatures between 60-70°. This resulted in a very dark colored liquid which was cooled to room temperature by standing, then acidified with 2 N. sulfuric acid and cooled under tap water.

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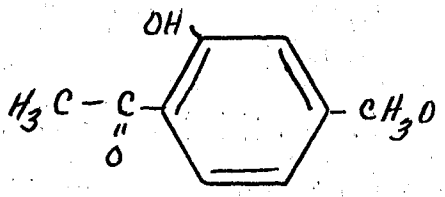
[8]N. M. Shah, Quinacetophenone Monomethyl Ether (Vol. XXXI of Organic Synthesis, ed. R. S. Schreiber. New York: Wiley and Sons, 1951), 90-91.

The mixture was then steam-distilled until no more oily drops were being collected in the condenser. After the distillate had sat overnight at room temperature, long, light green crystals were formed. It was filtered by suction, washed with cold water and air dried. M.p., 48-50°. (Reported yield, 55-64%).

Preparation of 2-Hydroxy-4-Methoxy Acetophenone[9]



Resacetophenone (25.0 g.) was added to 2 mls. of a 10% sodium hydroxide solution and the mixture stirred by hand gently until the dihydroxy was dissolved. Dimethylsulfate (2.1 g.) was added and the mixture heated to 90° and agitated for ten minutes. A minimum amount of sodium hydroxide was added, the solution was heated to 90° and shaken again. The solution was acidified with 10 ml. of hydrochloric acid, extracted with benzene, and the benzene solution was dried over a few grams of sodium sulfate (Na_2SO_4) for four hours.

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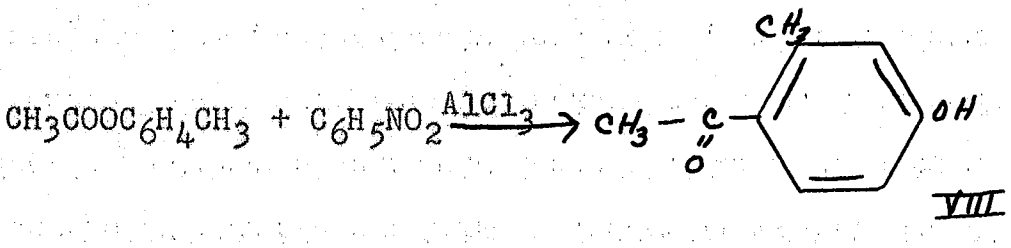
[9]Roger Adams, "Alkali-Insoluble Phenols," American Chemical Society Journal, XLI (1919), 247-70.

The solution was then filtered, and instead of the solvent being distilled off, it was evaporated via a rotating evaporator. The yellow product was not recrystalized by vacuum distillation due to an insufficient amount of material. M.p., 50°. Yield, 70-75%.

Preparation of 2-Methyl-4-Hydroxy Acetophenone[10]



VIII

Ortho-crecyl acetate (10 g.) was introduced into nitrobenzene (50 g.) in a flask, and to this mixture was added slowly 10 grams of aluminum chloride. Addition was controlled so that at no time did the reaction cause the temperature to rise above 60°c. The mixture was set for twenty-four hours at room temperature and then poured into ice and diluted hydrochloric acid (100 ml. of 18% HCl and a few cubes of ice). The mixture was transferred into a three-necked flask and steam distilled to remove the nitrobenzene. Distillation took four hours and the solvent was removed at a temperature of 200-215°. The dark product remaining was

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[10]A. H. Blatt, The Fries Reactions (Vol. I of Organic Reactions, ed. Roger Adams. New York: Wiley and Sons, 1942), 342-56.

vacuum-distilled at 39°c. and 30 mm. pressure. A colorless liquid (9 gms.) was obtained. M.p. of crude sample was 119° (reported yield 80-85% and m.p. of 128°).

II. SYNTHESIS OF CHALCONE DERIVATIVES

For this work, factors essential to preparation of chalcone derivatives by condensation of pyrrole-2-aldehyde with acetophenone and its derivatives were those governing the condensation reactions of aromatic ketones.

It was found that no one condensing reagent was sufficient for condensation of the various acetophenone derivatives and each derivative requires one specific reagent; an acidic, basic, alcoholic alkali, or combination of both an acid and a base. While not all the intermediates would condense to a chalcone derivative with one specific reagent, some would yield a chalcone with either an acid or a base. In such cases the products obtained vary in yields, m.p., and in their physical characteristics such as color.

Quantitative variation of any given reagent was relatively unimportant. This change would neither produce the reaction with an improper reagent, nor would it hinder the reaction with an appropriate agent.

The two most significant factors controlling the synthesis of these compounds were temperature and reaction time.

Considering the above experimental factors and the examination[11] of certain reported methods[12] of chalcone synthesis, the following four methods were devised and the reported compounds were made by one or all of the methods, as the need for establishing a fair degree of consistency between the yields and m.ps. would arise.

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[11]The following chalcones were prepared: 1) Benzal acetophenone, 2) 2-Hydroxy benzal acetophenone, 3) 3-Hydroxy benzal acetophenone, 4) 4-Hydroxy benzal acetophenone, 5) 2-4, Dihydroxy benzal acetophenone, 6) 2-2′, Dihydroxy benzal acetophenone, 7) 4-4′, Dihydroxy benzal acetophenone, 8) 5-Nitro-2-2′-dihydroxy benzal acetophenone, 9) 3-Hydroxy-(4′ methoxy-1′ chloro)-benzal acetophenone (reaction did not take place).

[12]Henry Gilman and Louis F. Cason, "Some Addition Reactions of Chalcones. (I) The Preparation of Some γ-Keto-sulfones," American Chemical Society Journal, LXXII (May, 1950), 3469-72; T. A. Geissman and S. L. Friess, "Flavanones and Related Compounds. (VI) The Polarographic Reductions of Some Substituted Chalcones, Flavones and Flavanones," American Chemical Society Journal, LXXI, Part 3 (December, 1949), 3893-902; Patrick F. Devitt, Anita Timoney, and Michael A. Vickory, "Synthesis of Heterocyclic-Substituted Chromones and Chalcones," Journal of Organic Chemistry, XXVI (December, 1961), 4941-44; Kamalahar B. Rant and Simon H. Wender, "A Synthesis of Certain Chalcones and 3-Hydroxy Chromones," Journal of Organic Chemistry, XXV (January, 1960), 50-52; Z. S. Ariyan and H. Suschitzky, "Heterocyclic Compounds of Chalcone Type," Journal of Chemical Society, (May, 1961), 2242-44; A. H. Williams, "Dihydrochalcones of Malus Species," Journal of Chemical Society (September, 1961), 4133-36; Cy. Sipos and Th. Szell, Naturwissenschaften 46, 532 (1959). Chemical Abstracts, LIV (1960), 6645, "Regarding the Possibility of the Formation of the Dypnones During the Preparation of Nitro-hydroxy Chalcones"; Roger Adams and John R. Johnson, Organic Chemistry (New York: The Macmillan Co., 1953), 375; Ben M. Benjamin and Clair J. Collins, "Molecular Rearrangement. (VIII) A Mechanistic Correlation of the Aldehyde-ketone and Pinacol Rearrangements," American Chemical Society Journal, LXXVIII (September, 1956), 4329-37.

Method I

Absolute alcohol (5 ml.) was placed in a 50 ml. flask and an equimolar quantity (0.01 mole) of freshly prepared ketone and the aldehyde was added. The flask was stoppered and shaken vigorously for one hour. To this solution was added dropwise 10 ml. of a 10% condensing agent (sodium hydroxide, sodium-methoxide, potassium hydroxide, or a 1:1 ethanoic 10% sodium hydroxide), during which the flask was shaken continuously. The flask was stoppered and allowed to sit for twenty-four hours or longer. Then ice water was added and the mixture acidified to congo red with 20% hydrochloric acid. The solution was then suction filtered and the precipitate collected in a filter paper. The precipitate was crystallized from ethanol.

Method II

Absolute alcohol (5 ml.) was placed in a 50 ml. flask together with 10 ml. of a 10% sodium hydroxide. This solution was mixed thoroughly, combined with 0.01 mole. of the ketone, and cooled in an ice-bath for one-half hour. The mixture was shaken thoroughly while 0.01 mole. of the appropriate aldehyde, cooled previously, was added. The agitation was continued for two hours, and then the flask was allowed to sit for two hours at a temperature between 10-30^{o} with an occasional agitation. The flask was then put in an ice-bath for

a period of one to four hours. The resulting product was suction filtered and the precipitate washed with cold water until the washings were neutral to litmus paper. Cold ethyl alcohol was used for crystallization.

Method III

a) Equimolar quantities (0.01 mole.) of the ketone and the aldehyde were placed in a 50 ml. flask and 20 ml. of water added. This solution was agitated for one-half hour and heated over a small flame. A minimum of sodium hydroxide-ethyl alcohol solution was added and the heating continued until a precipitate was formed. The heating was then discontinued and the flask allowed to sit for two to five minutes before the product was suction filtered. The precipitate is crystallized from ethanol.

b) The ketone (0.01 mole.) was dissolved in 10 ml. of 20% sodium hydroxide and mixed with 0.01 mole. of the aldehyde in minimum amount of absolute alcohol. The mixture was heated on a steam bath, acidified with hydrochloric acid and suction filtered. The product was washed with cold water until the washings were neutral to litmus paper. Alcohol was used for crystallization.

Method IV

Equimolar quantities (0.05 ml.) of the ketone and aldehyde were dissolved in minimum absolute alcohol, combined,

stirred, and cooled to below 0°. While the stirring was continued, 10 ml. of 50% NaOH was added portionwise, then enough alcohol-water was added to dissolve any formed salts. The mixture was then heated on steam bath for three hours, cooled, stoppered, and allowed to sit at room temperature from one to four weeks. The mixture was gently agitated periodically and then diluted with ice water and acidified with hydrochloric acid to congo red. A semi-solid mass was formed which was washed with cold water and dried.

The ether extract of this compound failed to yield any crystals upon distillation, evaporation of the solvent, and subsequent crystallization efforts from alcohol and alcohol and water.

Synthesis of Derivatives

Pyrrole-2-al-acetophenone. Pyrrole-2-aldehyde (0.01 mole.) and acetophenone (0.01) were placed in a 50 ml. flask containing sodium hydroxide (5 ml.) and ethyl alcohol 2.5 ml.). The mixture was agitated for one hour and allowed to stand at room temperature for one week. Ice water was added and the mixture acidified with 20% HCl to congo-red. The precipitate was then filtered and washed with cold water and crystallized with alcohol, forming yellow crystals. Yield, 80%; m.p., 136-138°.

Pyrrole-2-al-(2′hydroxy)-acetophenone. Absolute alcohol (5 ml.) was placed in a 50 ml. flask and equimolar quantities (0.01 mole.) of pyrrole-2-aldehyde and ortho-hydroxy acetophenone were added. The solution was mixed well and sodium hydroxide (10 ml.) were added dropwise while the mixture was stirred continuously. The mixture was put in an ice bath for two hours and then allowed to sit at room temperature for twenty-four hours, then at cold temperature for an additional twenty-four hours. The product was filtered and the yellow precipitate was washed with ice-cold water to crystallize from alcohol. Yield, 62%; m.p., 158-161°.

Pyrrole-2-al-(2′,4′-dihydroxy)-acetophenone. Absolute alcohol (5 ml.) and a 10% sodium hydroxide (10 ml.) were placed in a 50 ml. flask and mixed thoroughly. To this mixture was added 2,4-dihydroxy acetophenone (0.01 mole.) and the flask cooled in ice-bath for one-half hour. The mixture was shaken while pyrrole-2-aldehyde (0.01 mole.), which had been previously cooled in an ice-bath, was added. The solution was then agitated for an additional two hours and allowed to sit for four hours at temperatures between 10°c. and 30°c. The resulting product was filtered with suction and the precipitate washed with cold water until the washings were neutral to litmus paper. The red precipitate was crystallized from cold ethyl alcohol. Yield, 80%; m.p., 145-146°.

Pyrrole-2-al-(2',5'-dihydroxy)-acetophenone. Pyrrole-2-aldehyde (0.01 mole.) and 2,5-dihydroxy acetophenone (0.01) were combined in a 50 ml. flask and 20% sodium hydroxide (5 ml.) added dropwise. The flask was agitated for one-half hour and allowed to sit at room temperature for forty-eight hours. Ice-water was added and the solution acidified with HCl to congo-red. The orange precipitate was filtered and washed with cold water. Alcohol was used for crystallization, which gave a yield of 66%, m.p., 180-184°.

Pyrrole-2-al-(2'-methyl-4'-hydroxy)-acetophenone. Equimolar quantities (0.01 mole.) of pyrrole-2-aldehyde and 2-methyl-4-hydroxy acetophenone were placed in a 50 ml. flask and water (20 ml.) was added. The flask was agitated for one-half hour and heated over a small flame. A minimum amount of sodium hydroxide-ethyl alcohol solution was added and the mixture heated until a precipitate was formed. The heating was then discontinued and the flask allowed to stand for one or two minutes before the red precipitate was suction filtered. A yield of 26% was realized, with a m.p. of 179-180°.

Pyrrole-2-al-(2'-hydroxy-4'-methoxy)-acetophenone. Sodium hydroxide (5 ml.) and absolute alcohol (2.5 ml.) were placed in a 50 ml. flask. To this reagent was added 0.01 mole. of pyrrole-2-aldehyde and 0.01 mole. of 2-hydroxy-4-methoxy acetophenone. This solution was mixed thoroughly

for one-half hour and allowed to stand in an ice-bath for four hours with an occasional stirring. The temperature was then lowered to 5-0°c. and the flask kept at this temperature for forty-eight hours. The product was filtered and washed with cold water. Yellow crystals from alcohol gave a yield of 25%, m.p., 109-113°.

Pyrrole-2-al-(3-nitro)-acetophenone. M-nitroacetophenone (0.01 mole.) and pyrrole-2-aldehyde (0.01 mole.) were placed in a 50 ml. flask containing 10% sodium hydroxide (5 ml.) and absolute alcohol (2.5 ml.). The flask was shaken vigorously for one-half hour and allowed to stand at a temperature of 5-0° for twenty-four hours. Ice water was then added to the mixture and the solution acidified with 20% HCl to congo red. The solution and precipitate were filtered with suction. Crystallization of the precipitate from alcohol yielded (32%) a yellowish product, m.p., 72-75°.

Pyrrole-2-al-(2-hydroxy-5-methoxy)-acetophenone. Sodium hydroxide (5 ml.) and absolute alcohol (2.5 ml.) were placed in a 50 ml. flask. To this reagent was added 0.01 mole. of pyrrole-2-aldehyde and 0.01 mole. of 2-hydroxy-4-methoxy acetophenone. This solution was mixed thoroughly for one-half hour and allowed to stand in an ice-bath for four hours with an occasional stirring. The temperature was then lowered to 5-0°c. and the flask kept at this temperature

for forty-eight hours. The product was filtered and washed with cold water. Yellow crystals from alcohol gave a yield of 24%. M.p., 93-96°.

An attempt to react para-methoxy-w-chloro-acetophenone with pyrrole-2-aldehyde did not yield any chalcones.

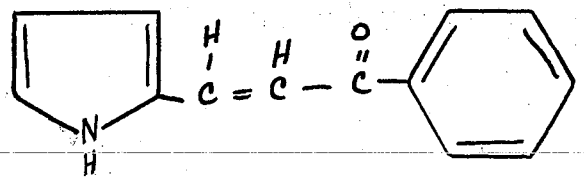
Figures of the compounds prepared are shown on pages 44 and 45.

FIGURE I

CHALCONE DERIVATIVES FROM

PYRROLE-2-ALDEHYDE

I.



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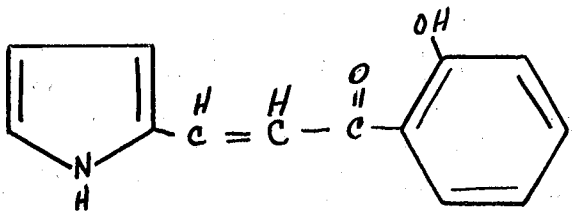

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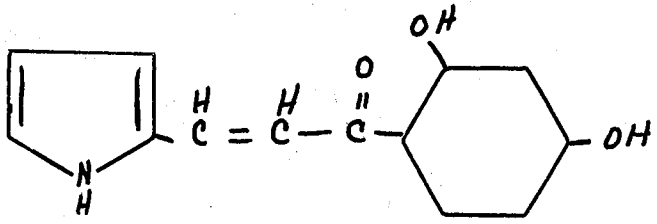

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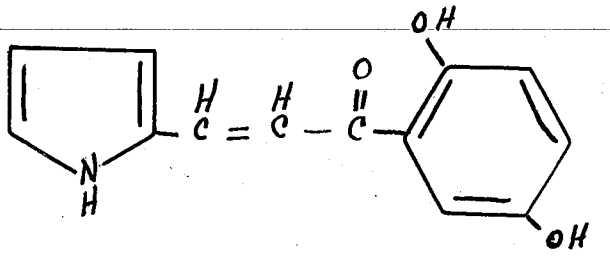
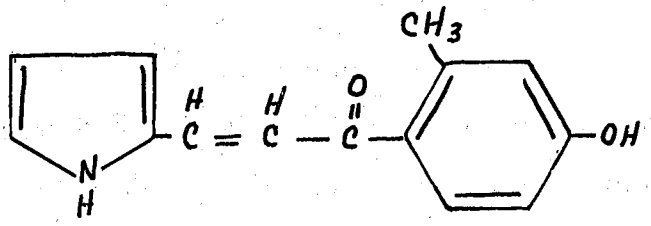
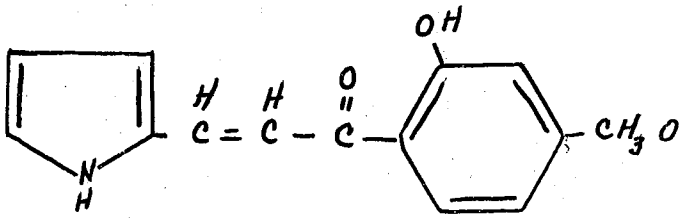


FIGURE I(continued)

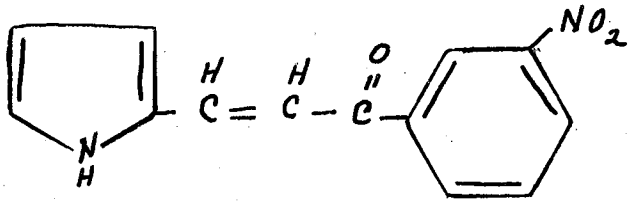
V.



VI.



VII.



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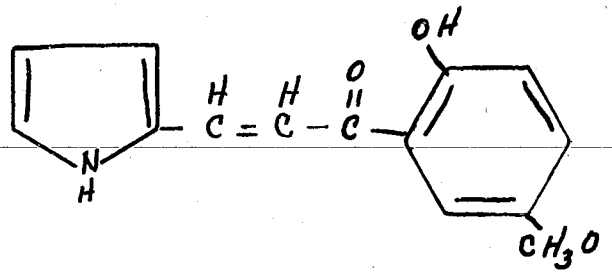

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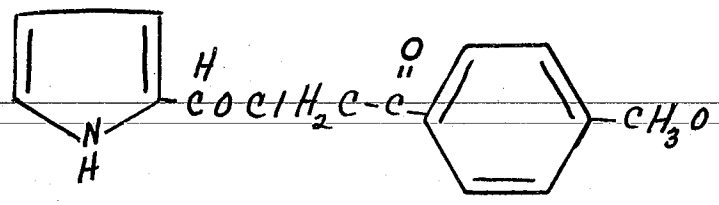

TABLE I

COMPOUNDS

	Compound
I.	Pyrrole-2-al-acetophenone
II.	Pyrrole-2-al-(2′-Hydroxy) acetophenone
III.	Pyrrole-2-al-(2′-4′-di-Hydroxy) acetophenone
IV.	Pyrrole-2-al-(2′,5′-di-Hydroxy) acetophenone
V.	Pyrrole-2-al-(2′-methyl-4′-Hydroxy) acetophenone
VI.	Pyrrole-2-al-(2′-Hydroxy-4′-Methoxy) acetophenone
VII.	Pyrrole-2-al-(3′-nitro) acetophenone
VIII.	Pyrrole-2-al-(2′-Hydroxy-5′-Methoxy) acetophenone

CHAPTER VI

INFRA-RED SPECTRA OF THE INTERMEDIATES AND CHALCONES

In infra-red spectroscopy, conjugation of a carbonyl group and double bonds causes a shift from the normal position to a longer wave length. Thus, conjugation of carbonyl group with one phenyl group, as in acetophenone, lowers the wave length to 1686^{cm-1}. If an ionic resonance structure such as $\rangle C^{\oplus}-O^{\ominus}$ can contribute to a carbonyl group such as $\rangle C=O$, a shift to lower frequency takes place.

In acetophenone when a hydroxyl group is introduced alpha to keto group, carbonyl frequency shifts from 1686^{cm-1} to 1635^{cm-1}. This is due to either hydrogen bonding between hydroxyl group and keto group,[1] or to a conjugate-chelate system. Ortho-hydroxy acetophenone spectrum of region $3500-2500^{cm-1}$ lacks any band due to a hydroxyl group and acetylation shifts the band back to 1686. Therefore, conjugated chelation is responsible for the shift to a shorter wave length. Ortho-methoxy acetophenone absorption band is at 1649^{cm-1}, and so there is neither hydrogen bonding nor

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[1] H. L. Hergert and E. F. Kurth, "The Infrared Spectra of Lignin and Related Compounds. (I) Characteristic Carbonyl and Hydroxyl Frequencies of Some Flavanones, Flavones, Chalcones and Acetophenones," American Chemical Society Journal, LXXV (1953), 1622-25.

chelation, and the lowering of the band is due to participation of resonance forms. In para-hydroxy acetophenone hydroxyl band is at 3250^{cm-1} caused by strong hydrogen bonding. The 2-4-dihydroxy derivatives of acetophenone require the same conditions as noted above. Due to increased electron supply, dimethoxy derivative shows a shift lower than ortho and para compounds. Meta-position is not conjugated with carbonyl groups, thus indicating that methoxyl group (even though electron donor) is in conjugated position to affect carbonyl group frequency.

In aromatic compounds the bands from a normal C=C link near 1640^{cm-1} are usually above the 1600^{cm-1} phenyl band,[2] but when conjugated with the ring, the C=C frequency often falls within the same absorption region. Aromatic-type compounds give rise to a large number of very sharp, characteristic bands. The changes in certain regions which result from substitution are often independent of the nature of the substitutions. Presence of an aromatic-type structure is best recognized by the presence of the =C-H stretching vibrations near 3030^{cm-1} and C=C vibrations in the 1600-1500^{cm-1} region. The presence and relative positions of

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[2] J. A. Mitchell, C. D. Bockman, and A. V. Lee, "Determination of Acetyl Content of Cellulose Acetate by Near Infrared Spectroscopy," Journal of Analytical Chemistry, XXIX, No. 4 (April, 1957), 499-502.

substituents can be studied in the regions 2000-1660^{cm-1}, 1250-1000^{cm-1}, and 100-650^{cm-1}. The first region is the most definite and gives a clear indication of the type of substitution. Strong electron attracting or donating substituents such as nitro-groups exert a profound influence on all these three regions. Confirmation of an aromatic structure is obtained from the 1600-1500^{cm-1} region.

In aromatic compounds, one of the ring doublebonds can function as the α,β-unsaturated unit, and 1-keto-2-hydroxy compound show abnormal carbonyl frequencies. In acetophenones with large substituents at the ortho-position the carbonyl group can rotate out of the plane of the ring and then the frequency rises. Carbonyl absorption of ortho-hydroxy acetophenone is at 1639-1613^{cm-1}, while that of acetophenone is 1686^{cm-1}.

When an aryl group is directly attached to the carbon atom of a carbonyl group, the frequency shift of the carbonyl is less than that occurring with a full double bond in conjugation and absorption band occurs in the range 1700-1680^{cm-1}.

Benzal acetophenone which has an aliphatic double bond and aryl ring in conjugation with the CO group, absorbs at 1667^{cm-1}, para-hydroxy acetophenone at 3250^{cm-1}, acetophenone in condensed phase at 1707^{cm-1}. As stated before, substitution of -OH-group on the ring alpha to the

carbonyl group is due to chelation. Other substituents on the ring affect the frequency also; the substitution of alkyl groups in the ortho positions results in a shift to higher frequency, due to the reduction in the degree of coplanarity which the carbonyl group can achieve with the ring. The carbonyl frequencies of the substituted acetophenone vary over a considerable range, depending upon the electron attracting or repelling properties of the substituent groups.

Observed carbonyl frequencies of acetophenone can be correlated directly with the Hammett σ— values of the substituents (σ— values are a direct measure of the electron donation or withdrawal produced by the substituent group). In some cases the 1600^{cm-1} region band becomes so strong, having a greater intensity than that of a carbonyl group with which it is conjugated; this occurs, for instance, in spectra of solutions of para-hydroxy acetophenone, while ortho-hydroxy acetophenone exhibits broad weak OH absorption bands extending from 3500^{cm-1} beyond 2900^{cm-1} and with ketonic group gives $3320\text{-}3340^{cm-1}$. In 5-hydroxy acetophenones no frequency shift occurs, but in 3-hydroxy acetophenones there is a fall of 30^{cm-1} frequency shift.

In ketones the frequency of the carbonyl absorption is determined by the nature of its immediate environments. In α,β-unsaturated ketones, the carbonyl frequency shifts

TABLE II

CARBONYL FREQUENCIES OF ACETOPHENONE DERIVATIVES

Compound	C=O Frequency in cm^{-1}
Acetophenone	1686
Ortho-hydroxy acetophenone	1635
Para-hydroxy acetophenone	1633
Metha-hydroxy acetophenone	1620
Para-methoxy acetophenone	1642
Ortho-methoxy acetophenone	1649
Metha-nitro acetophenone	1701
2-4-di-hydroxy acetophenone	1638
2-5-di-hydroxy acetophenone	1635
2-hydroxy-4-methoxy acetophenone	1615
Para-amino acetophenone	1677
Para-chloro acetophenone	1692
Para-bromo acetophenone	1693
Para-nitro acetophenone	1702
Para-acetoxy acetophenone	1691
Para-acetyl amino acetophenone	1686
5-Hydroxy amino acetophenone	1653

away from the normal position. Frequency shifts due to chelation and interference effects also occur. Also, some shifts arise due to hydrogen bonding effects and from changes of state.

Five membered ring ketones show frequency shifts on conjugation[3] and α,β-unsaturated C=O group absorbs at 1716^{cm-1} (same as in α,β-unsaturated ketones).

Infra-red spectral frequencies of various compounds reported in literature seem to be not in complete agreement and comparison of several sources concerning absorption frequencies of any one compound should be taken into consideration.

The following data[4] in a tabulated form concerning aromatic compounds, $\alpha-\beta$ unsaturated ketones and chalcones, will conveniently aid the interpretation of the infra-red spectra of the intermediates and the chalcones.

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[3]J. H. Ross, "Infrared Spectra for Analysis of Aldehyde and Ketone 2,4-Dinitrophenylhydrozones," Journal of Analytical Chemistry, XXV, No. 9 (September, 1953), 1288-1303; R. L. Powell, N. E. Fuson, et al, "The NH Stretching Vibration and NH-N Hydrogen Bonding," Journal of Chemical Physics, XX, No. 1 (January, 1952), 145-52; N. Fuson and M. Josien, "Infrared Study of the Effect of Solvent upon (NH) in Pyrrole," Journal of Chemical Physics, XXII, No. 7 (July, 1954), 1169-76.

[4]H. M. Randall, et al, "Infra-red Determination of Organic Structures." (New York: D. VanNostrand Co., Inc., 1959), 39, 42, 166, 221; L. J. Bellamy, "The Infra-red Spectra of Complex Molecules." (New York: Wiley and Sons, 1958), Ch. 2,3,5,6 and 9; G. E. Inglett, "Infra-red Spectra of Some Naturally Occurring Flavonoids," Journal of Organic Chemistry, XXIII (January, 1958), 93-94; J. H. Looker and Walter W. Hanneman, "Physical and Chemical Properties of Hydroxy-

I. AROMATIC COMPOUNDS AND KETONES

=C-H Stretching-Modes[5]

Sharp absorption near 3030^{cm-1} (3040-3010^{cm-1})

2000-1660 $^{cm-1}$.

C=C Skeletal In-plane vibrations.

Near 1600^{cm-1} (v).

Near 1500^{cm-1} (v).

Near 1580^{cm-1} (n)-conjugated rings.

Near 1450^{cm-1} (n).

CH Out-of-plane deformations.

Five adjacent free hydrogen atoms 770-730^{cm-1} (vs)

and 710-690^{cm-1} (s).

Four adjacent free hydrogen atoms 770-735^{cm-1} (vs).

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flavones. (I) Infrared Absorption Spectra of Monohydroxy Flavones and their O-Methyl and O-Acetyl Derivatives," Journal of Organic Chemistry, XXVII (February, 1962), 381-89; J. H. Looker and W. W. Hanneman, "Physical and Chemical Properties of Hydroxy Flavones. (II) 3-Aroyl-5-Hydroxy Flavones. Synthetic and Infrared Spectral Studies," Journal of Organic Chemistry, XXVII (September, 1962), 3261-63; R. Percy Barnes and G. E. Pinkney, "Absorption Spectra of Some γ- and β-Di-ketones," American Chemical Society Journal, LXXV, Part 1 (1953), 479-80; G. F. Sovatos, Columba Curran, and J. V. Quagliano, "Infrared Absorption Spectra of Inorganic Coordination Complexes. (V) The N-H Stretching Vibration in Coordination Compounds," American Chemical Society Journal, LXXVII, Part 4 (1955), 6159-63; H. W. Thompson and P. Torkington, "The Vibrational Spectra of Esters and Ketones," Journal of Chemical Society, (October, 1945), 640-45.

[5]Ibid. (Randall, et al; Bellamy; Inglett; and Looker and Hanneman.

Three adjacent free hydrogen atoms 810-750^{cm-1} (vs).

Two adjacent free hydrogen atoms 860-800^{cm-1} (vs).

One free hydrogen atom 900-860^{cm-1} (m).

The region 1225-950^{cm-1}.

1:2, 1:4, and 1:2:4--substitution 1225-1175^{cm-1} (w).

1125-1090^{cm-1} (w).

1070-1000^{cm-1} (w).

Mono, 1:3, 1:2:3, and 1:3:5--

Substitution 1175-1125^{cm-1}.

1110-1070^{cm-1}.

N-H Stretching Band near 3080^{cm-1}.

CH_3-2962^{cm-1} and 2872^{cm-1} $\pm$ 10 (s).

C-H Deformation frequency.

CH_3O at 1466^{cm-1}.

$C-CH_3$:1450^{cm-1} $\pm$ 20 (m) asymmetrical

1380 - 1370^{cm-1} (s) asymmetrical

near 1340^{cm-1} (w).

Non-conjugated C=C stretching vibration 1680-1620^{cm-1}.

Phenyl conjugated C=C stretching vibration near 1625^{cm-1}.

-CH=CH (trans.):3040-3010^{cm-1} (m) - stretching.

970-960^{cm-1} (s) CH out-of-plane deformation.

(cis.):1340-1295^{cm-1} (sw) CH in-plane deformation.

3040-3010^{cm-1} (m) CH stretching.

near 690^{cm-1}, CH out-of-plane deformation.

C=O in $\alpha, \beta - \alpha', \beta'$ unsaturated aromatic ketones: 1685-1665^{cm-1}.

in chelated unsaturated aromatic ketones: 1640-1540^{cm-1}.

in conjugation with α aryl group: 1695-1686^{cm-1}.

in 5-membered ring ketones: 1750-1740^{cm-1}.

in 6-membered ring ketones: 1735-1700^{cm-1}.

in 1-keto-2-hydroxy ketones: 1655-1635^{cm-1}.

N-H stretching: 3500-3300^{cm-1} (m), 3300-3100^{cm-1} (s), and 1650-1550^{cm-1} (vw).

NO_2 groups: 1680-1610^{cm-1}.

C-NO_2 groups: 1570-1500^{cm-1} (s) and 1370-1300^{cm-1}.

-OH Stretch: 3650-3590^{cm-1} (v) sharp.

3625-3600^{cm-1} non-associated.

3550-2700^{cm-1} associated.

Phenolic OH deformation, CO stretching absorption: near 1206^{cm-1} (s) and 1410-1310^{cm-1} (s).

Alkyl ketones: 1325-1215^{cm-1} (s).

Aryl ketones: 1225-1075^{cm-1} (s).

<u>CO Vibrations in Aldehyde</u>

Saturated aliphatic: 1740-1720^{cm-1}.

α, β -unsaturated: 1705-1680^{cm-1}.

Aryl aldehydes: 1680-1660^{cm-1}.

C-H deformation vibrations:

All types: 980-975^{cm-1} (m).

Aliphatic aldehyde: 1440-1325^{cm-1} (s).

TABLE III

HYDROXYL FREQUENCIES

Compound	-OH in cm^{-1}
Para-hydroxy acetophenone	3250
Metha-hydroxy acetophenone	3220
2,4-di-hydroxy acetophenone	3260, 3150
2,5-di-hydroxy acetophenone	3250
5-hydroxy acetophenone	3250

TABLE IV

CHALCONE COLOR REACTIONS

	H_2SO_4 From	H_2SO_4 To	NaOH	HCl
Compound I*	Y.	R.	N.R.	N.R.
Compound II	Y.	R.	N.R.	N.R.
Compound III	R.B.	Y.	D.R.	Y.
Compound IV	O.	R.	D.R.	N.R.
Compound V	R.	N.R.	N.R.	N.R.
Compound VI	R.	N.R.	N.R.	N.R.
Compound VII	Y.	N.R.	N.R.	N.R.
Compound VIII	R.	N.R.	N.R.	N.R.

Color Symbols: Y.= Yellow, R.= Red, O.= Orange, N.R.= no reaction, D.R.= deep red, R.B.= red brown

* See Table I, page 46.

TABLE V

SOLUBILITY IN VARIOUS SOLVENTS

Compound	Ethyl Alcohol	Ether	Acetone	Water
I.	S.	I.	S.	I.
II.	I.	I.	I.	SS.
III.	S.	S.	S.	I.
IV.	SS.	S.	S.	I.
V.	S.	S.	S.	I.
VI.	I.	I.	SS.	I.
VII.	S.	S.	S.	I.
VIII.	I.	I.	I.	I.

S. = Soluble
I. = Insoluble
SS. = Slightly soluble

CHAPTER VII

SUMMARY

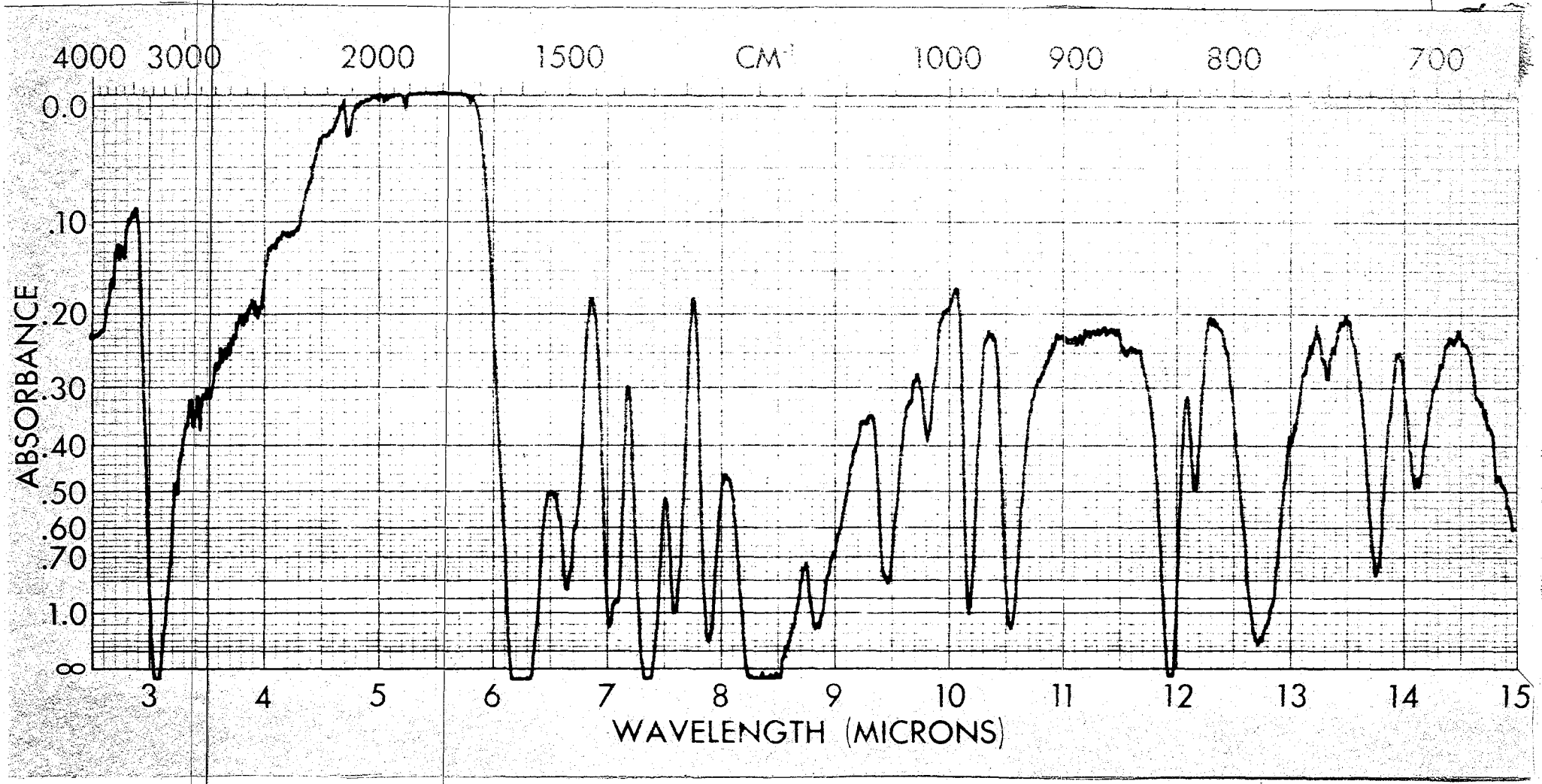
Derivatives of chalcones from pyrrole-2-aldehyde have been prepared. Acetophenone and its hydroxy derivatives gave good yields by various methods. Nitro and methyl derivatives were obtained in lower yield than the hydroxy compounds. Methoxy derivatives were also prepared in comparatively low yields.

An attempt to react para-methoxy-ω-chloro acetophenone with pyrrole-2-aldehyde did not yield a chalcone.

Several derivatives of benzalacetophenone were prepared by the same methods.

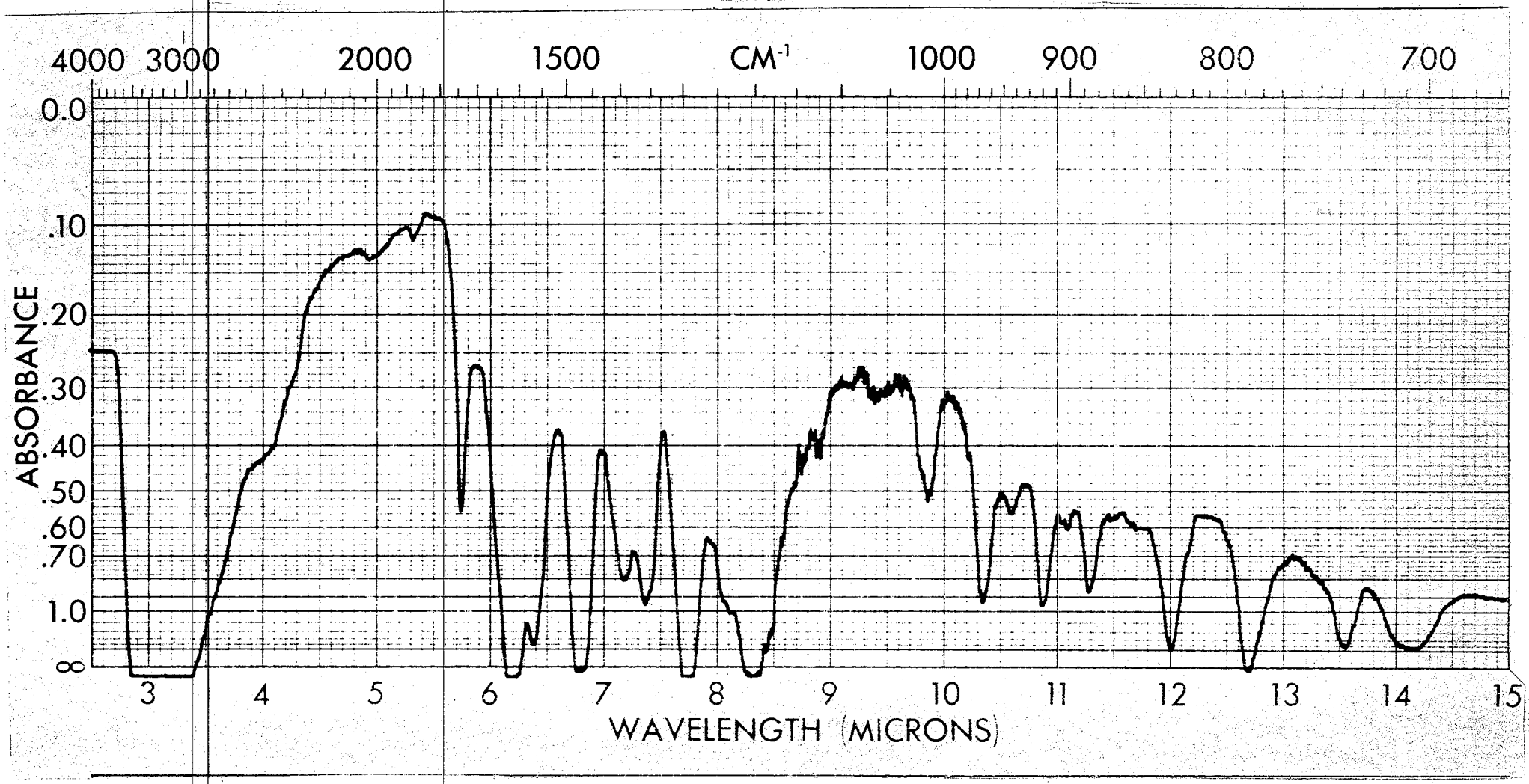
A correlation of melting point of each compound resulted by application of two or more methods. The spectra of the intermediates and chalcones, using Perkin-Elmer infrared Spectrophotometer, are reported. The color reactions, solubilities, yields, and melting points are also presented.

It is concluded that the best conditions for preparation of chalcone derivatives from pyrrole-2-aldehyde are near zero degrees temperature, twenty-four or more hours reaction time, and the use of an alcoholic-alkali condensing reagent.

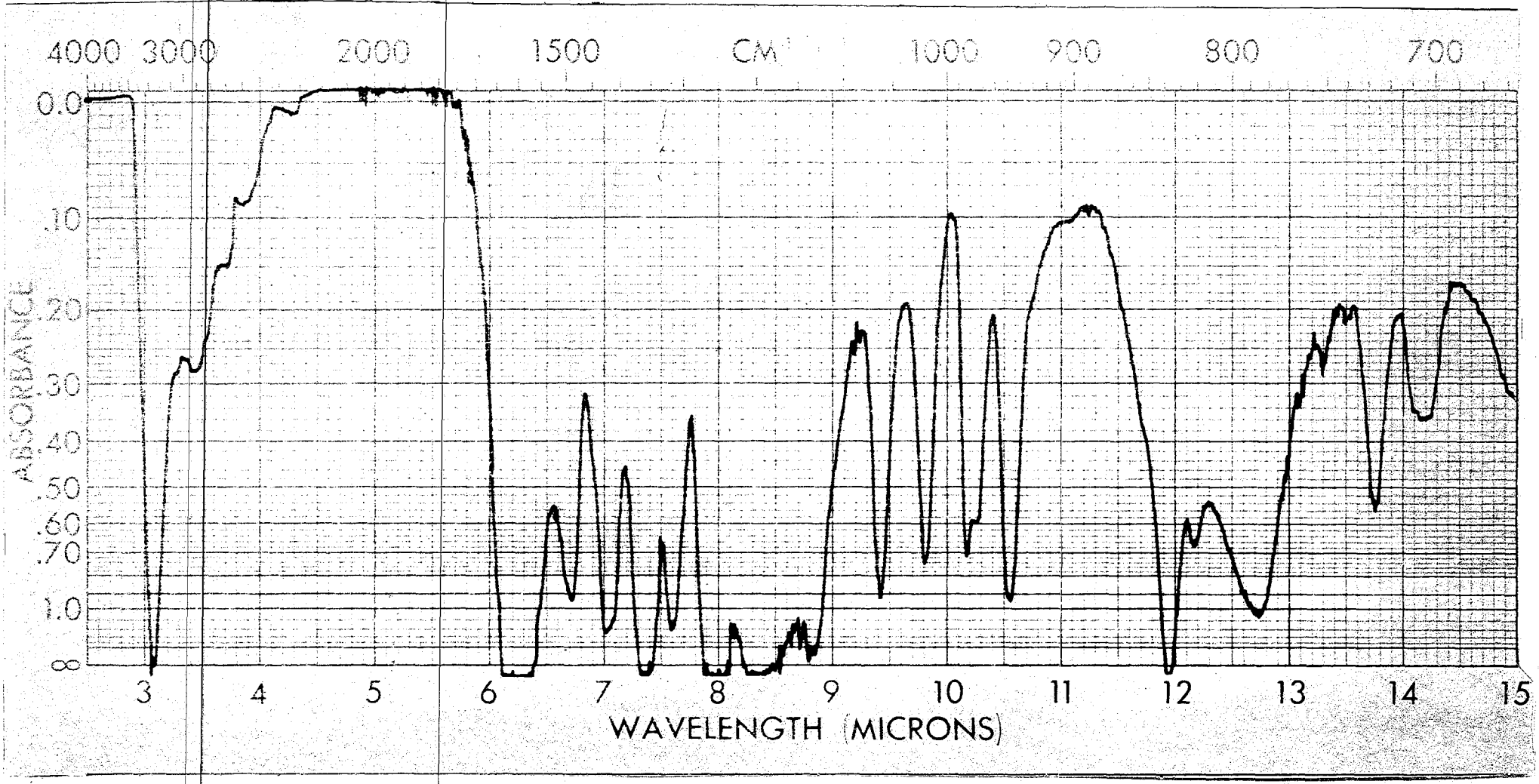


2, 4- DIHYDROXY ACETOPHENONE

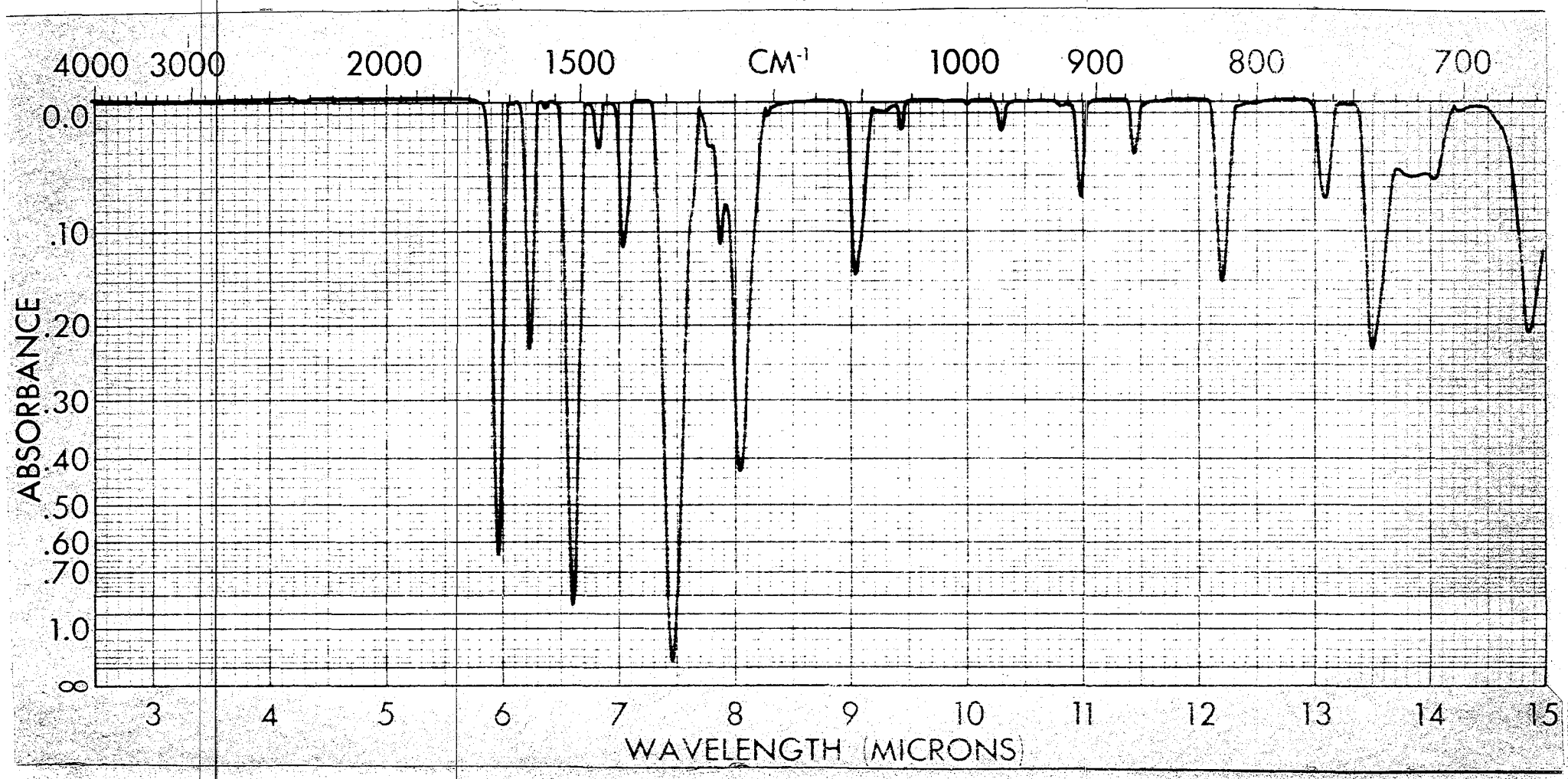
09



2, 5-DIHYDROXY ACETOPHENONE



2-HYDROXY-4-METHOXY ACETOPHENONE



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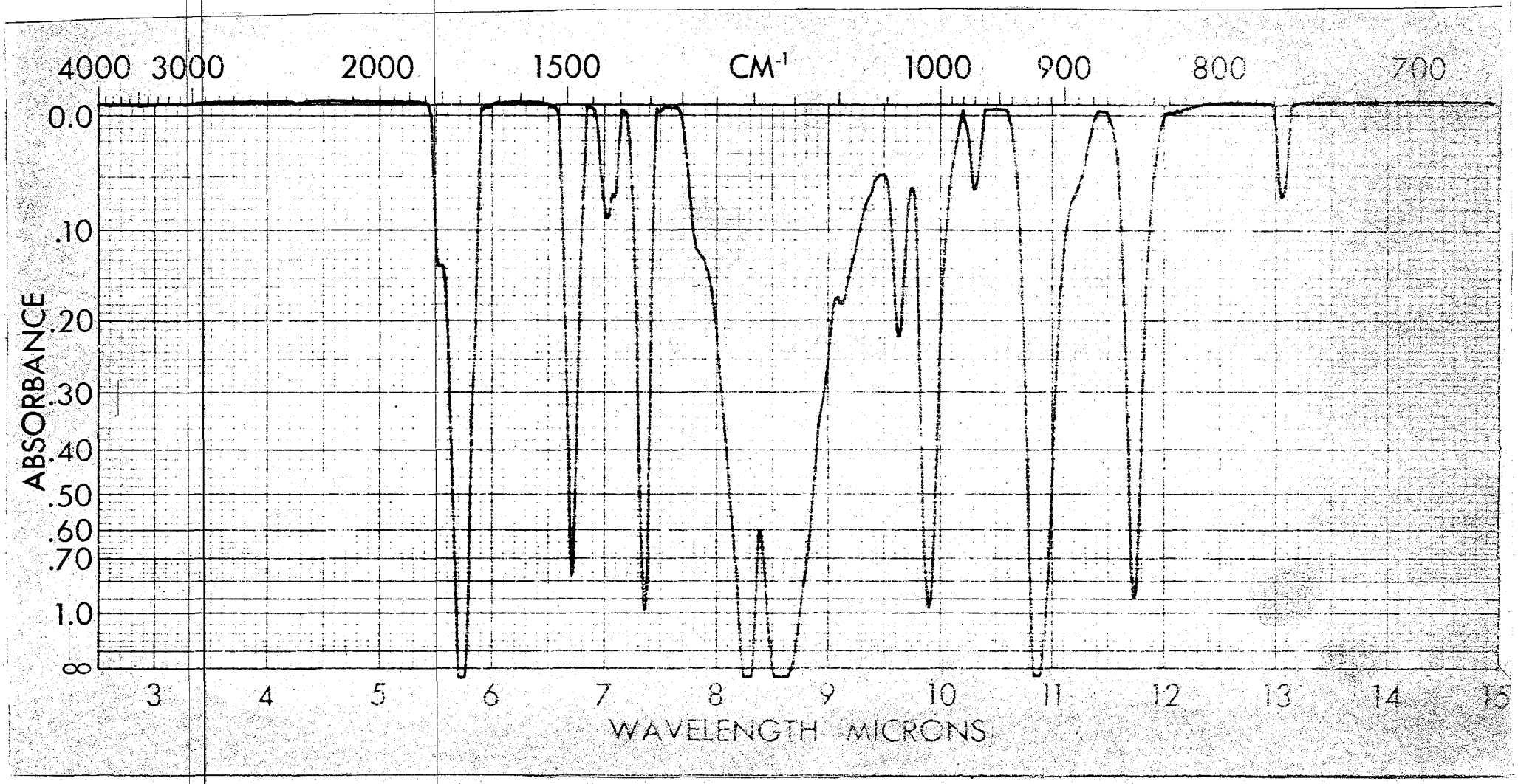
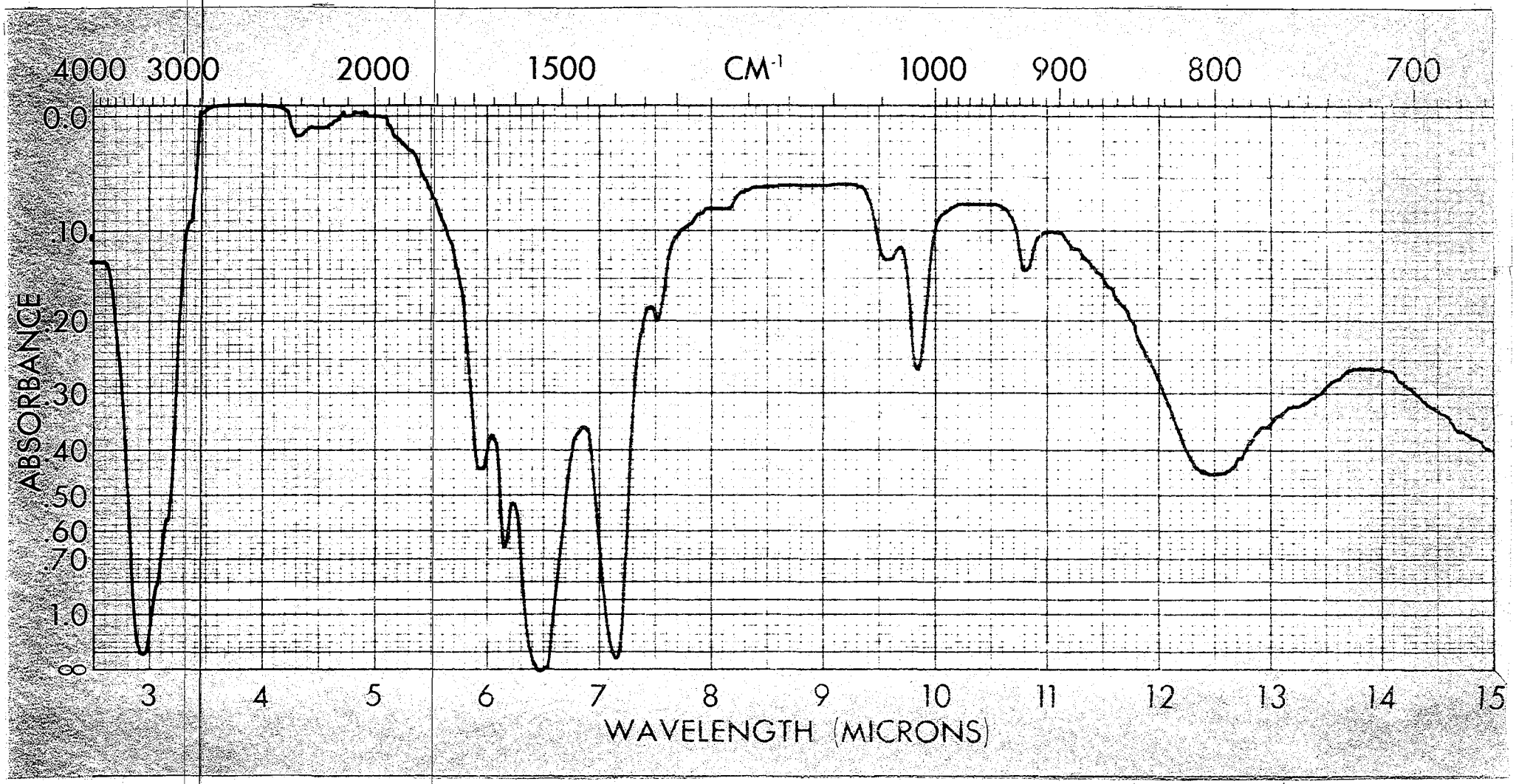
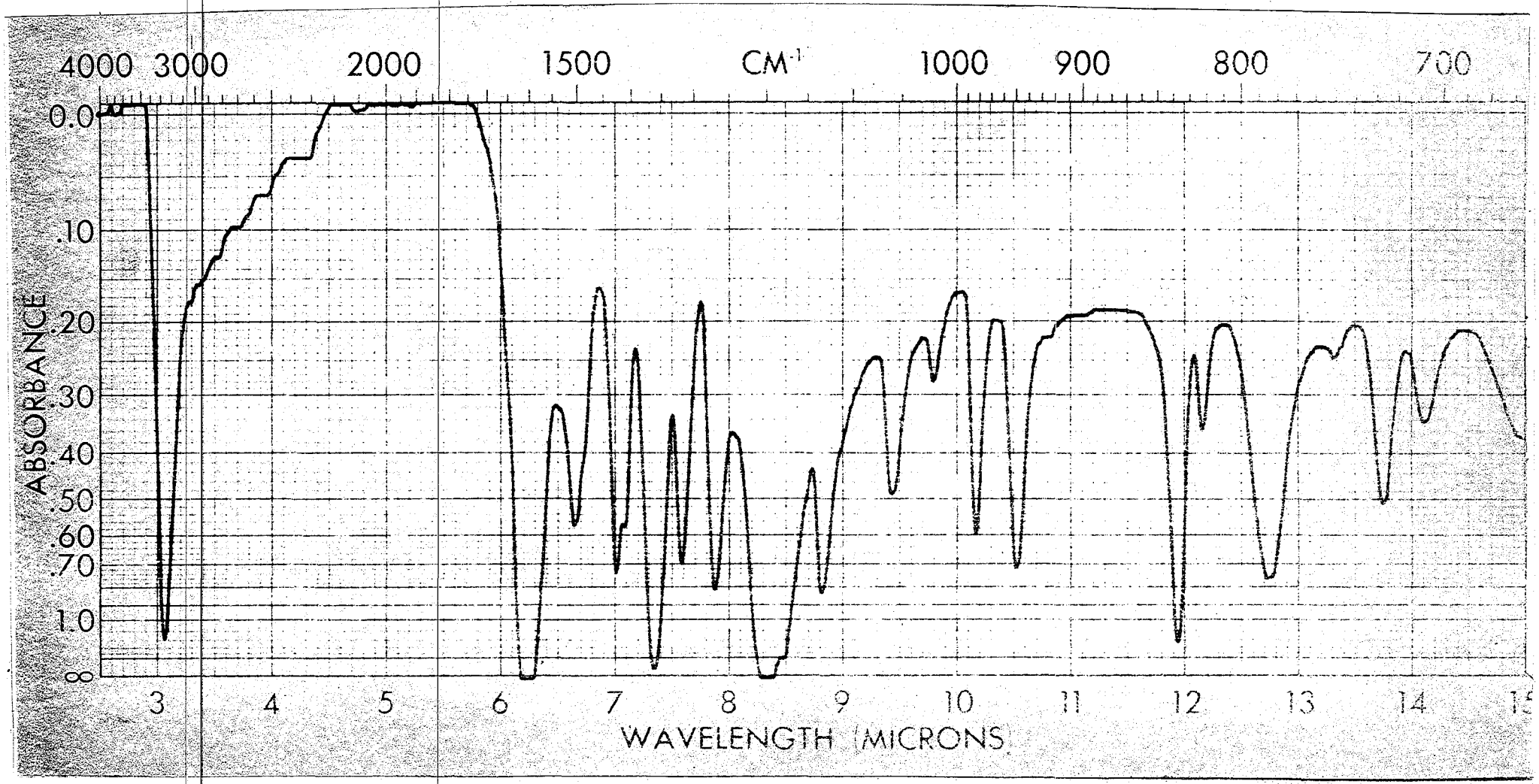


HYDROQUINONE DIACETATE

49



PYRROLE-2-ALDEHYDE



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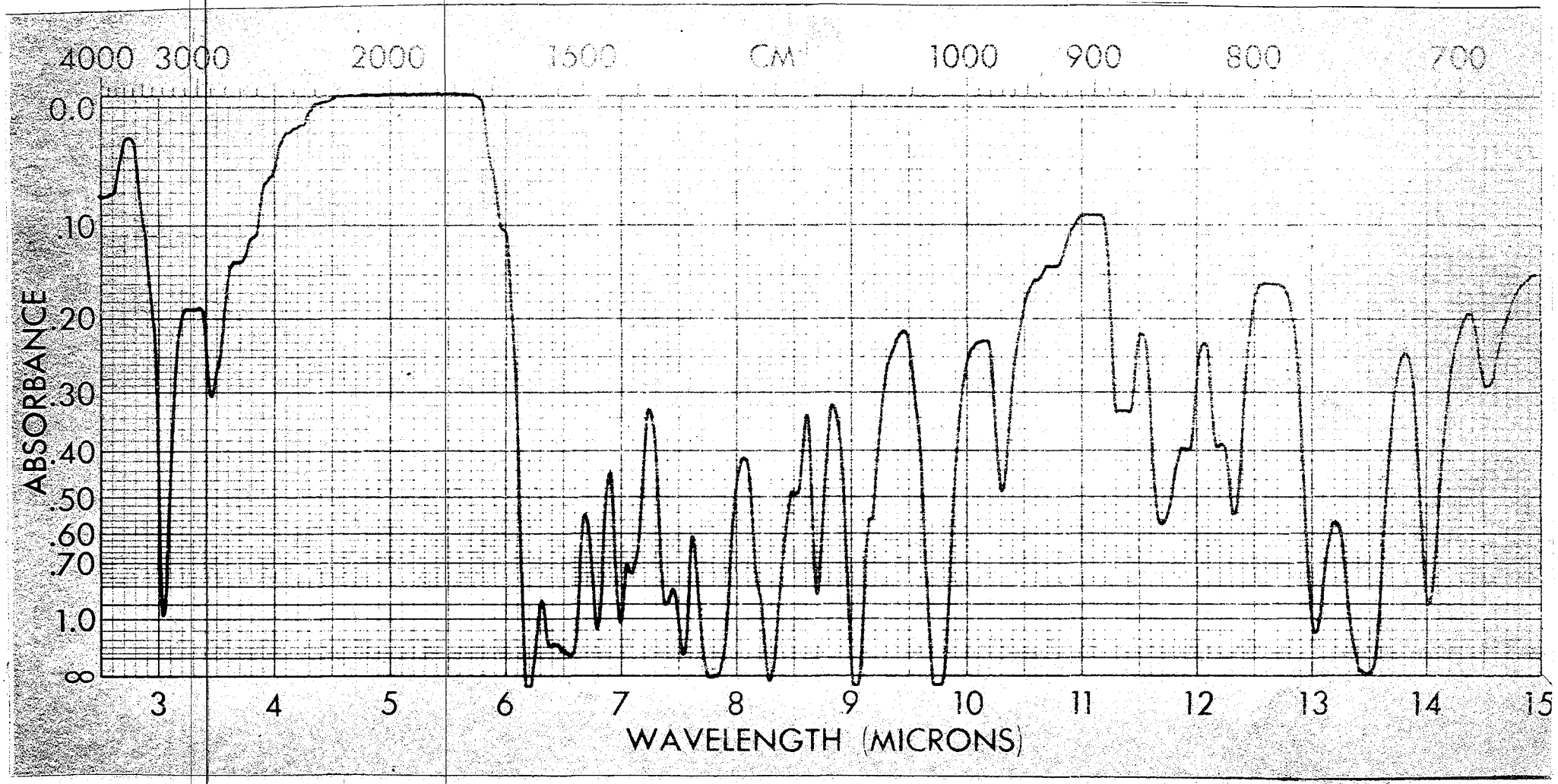

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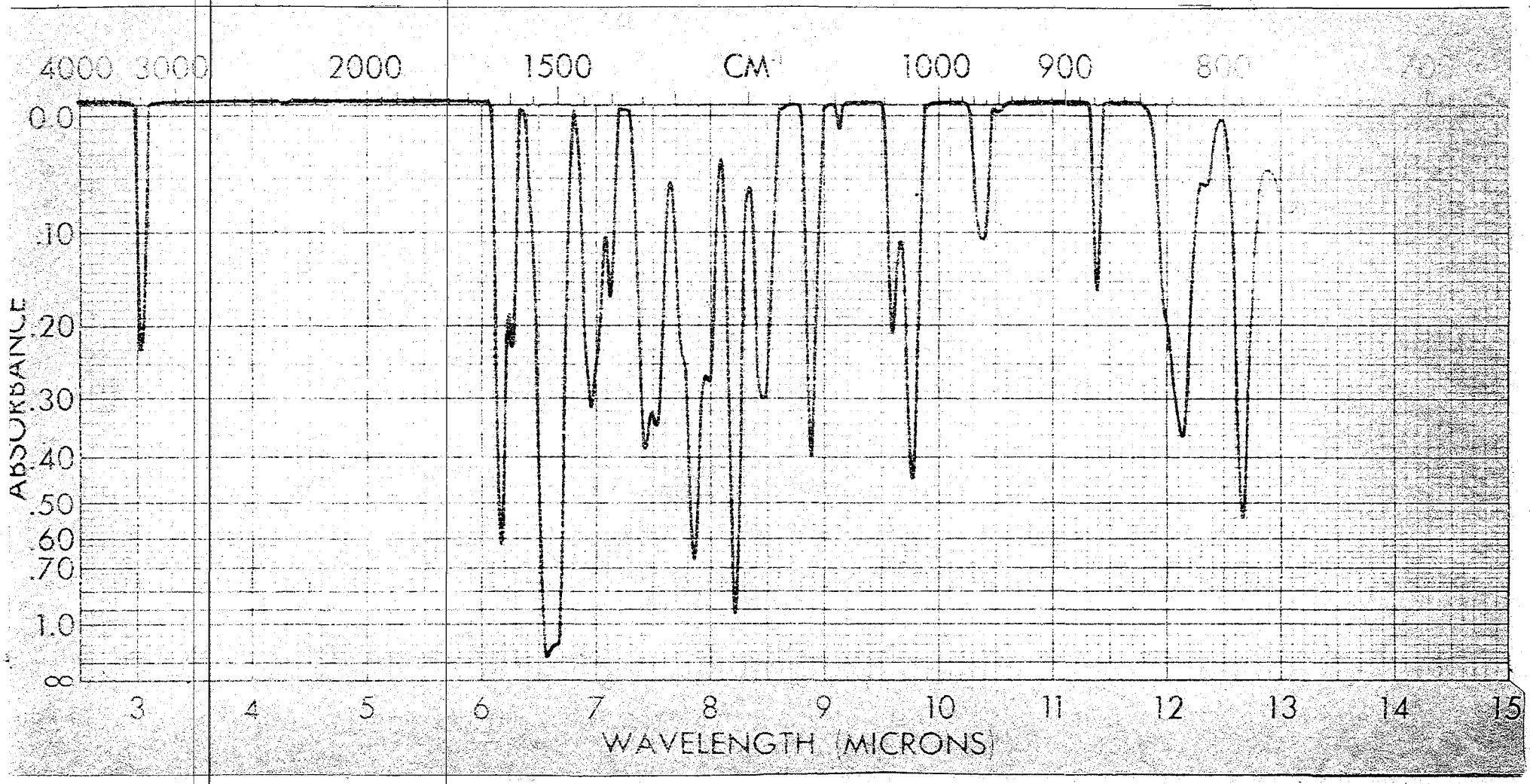

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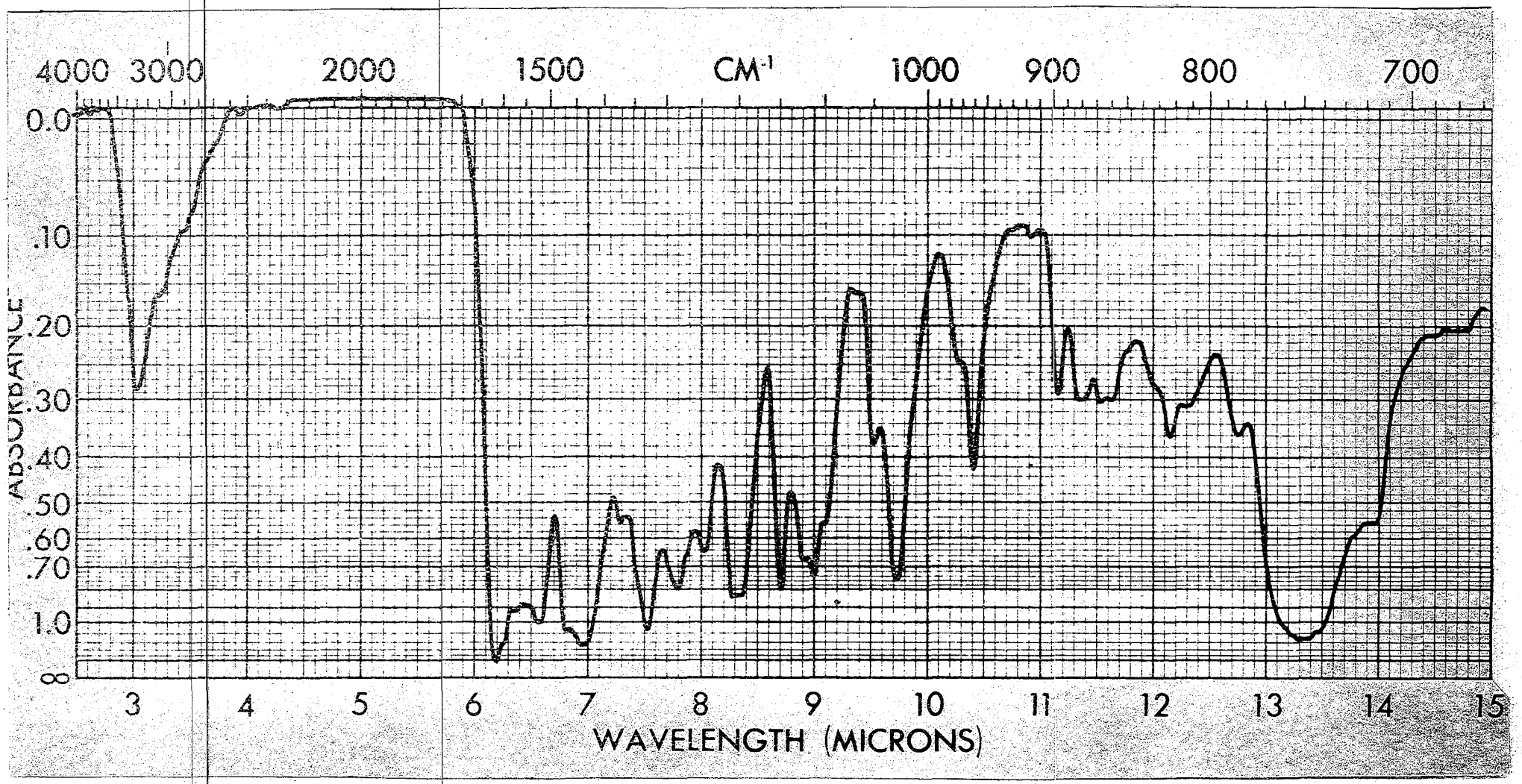

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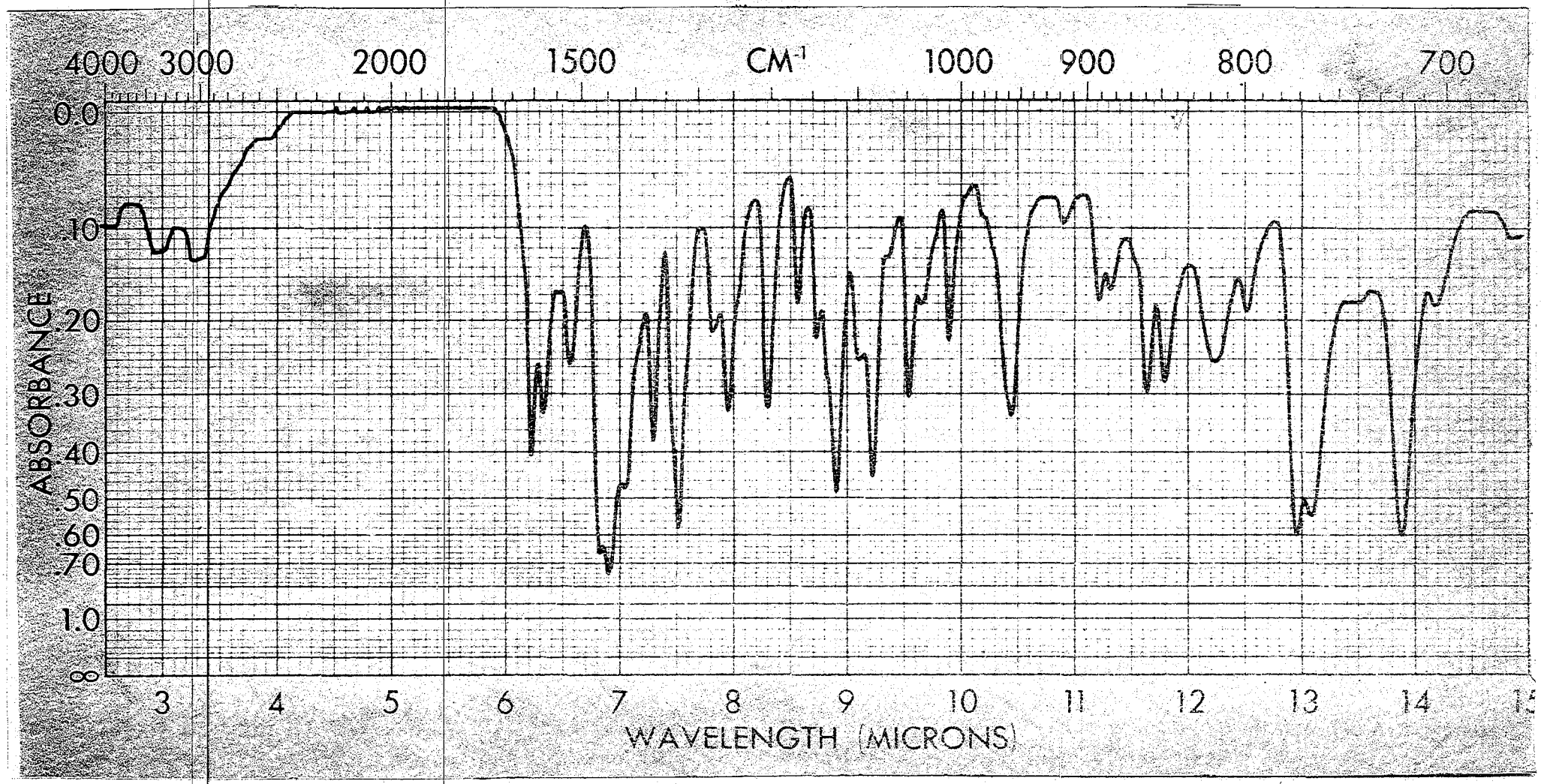

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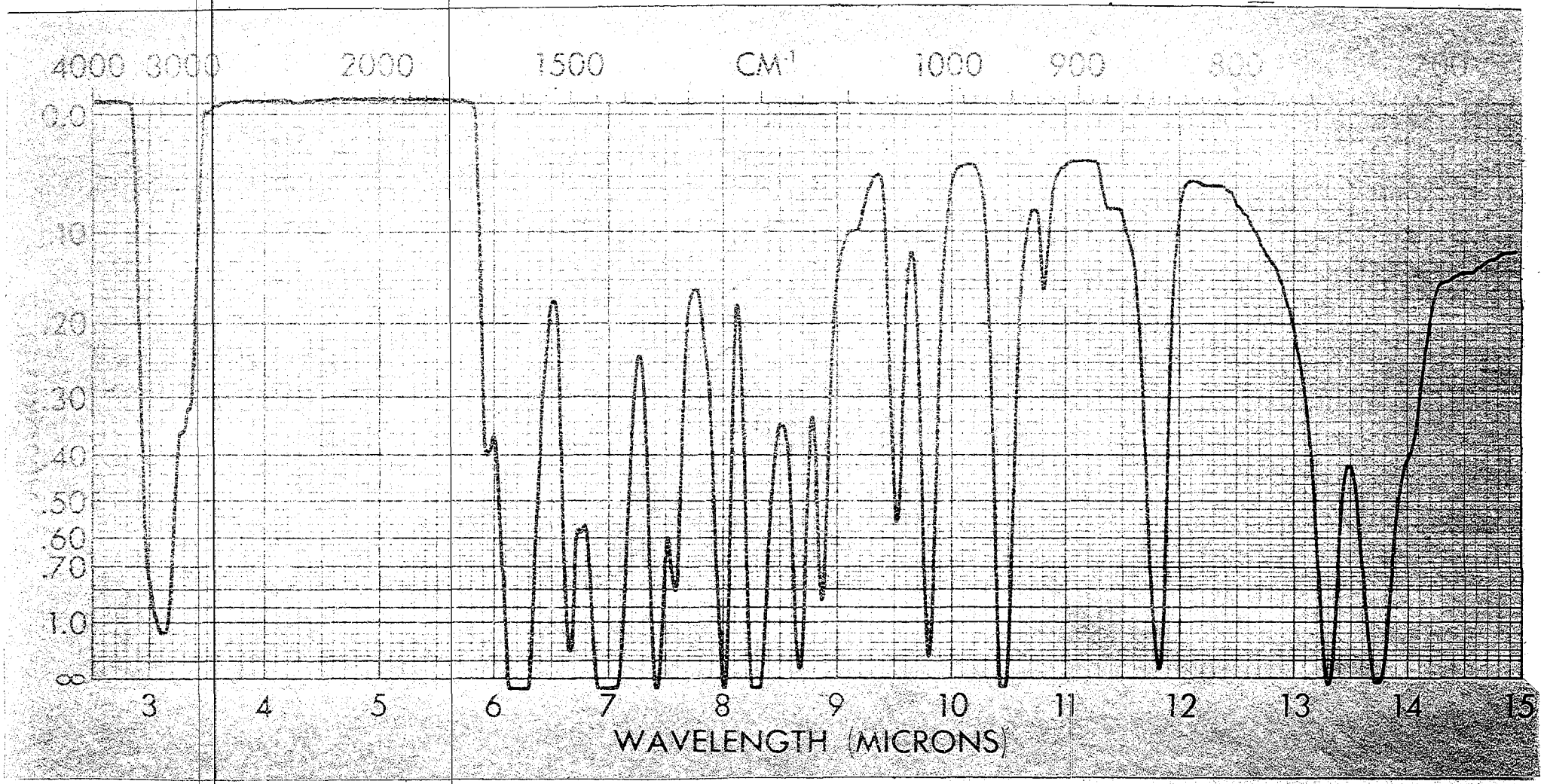
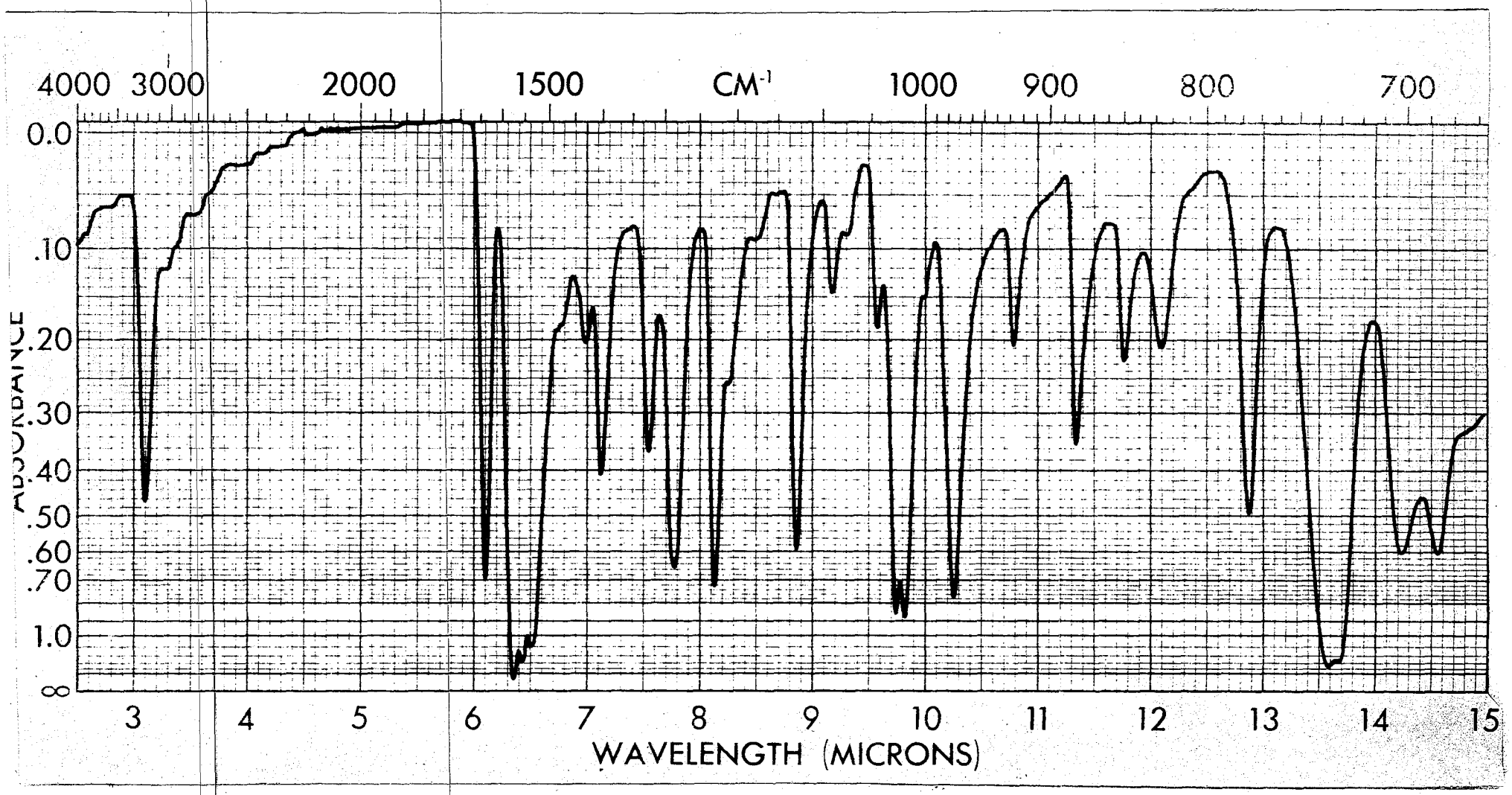


PYRROLE-2-AL(2'-HYDROXY) ACETOPHENONE

11



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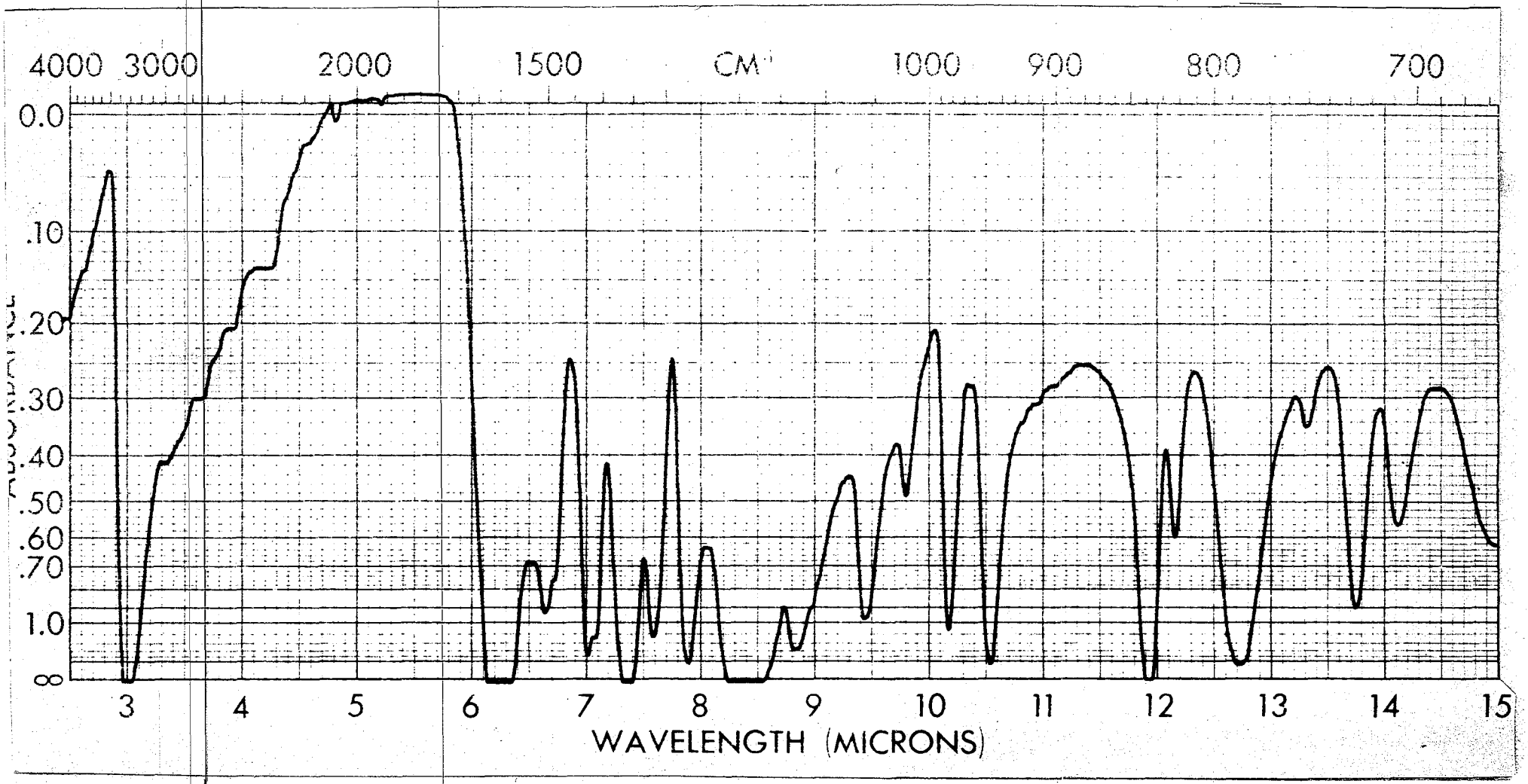
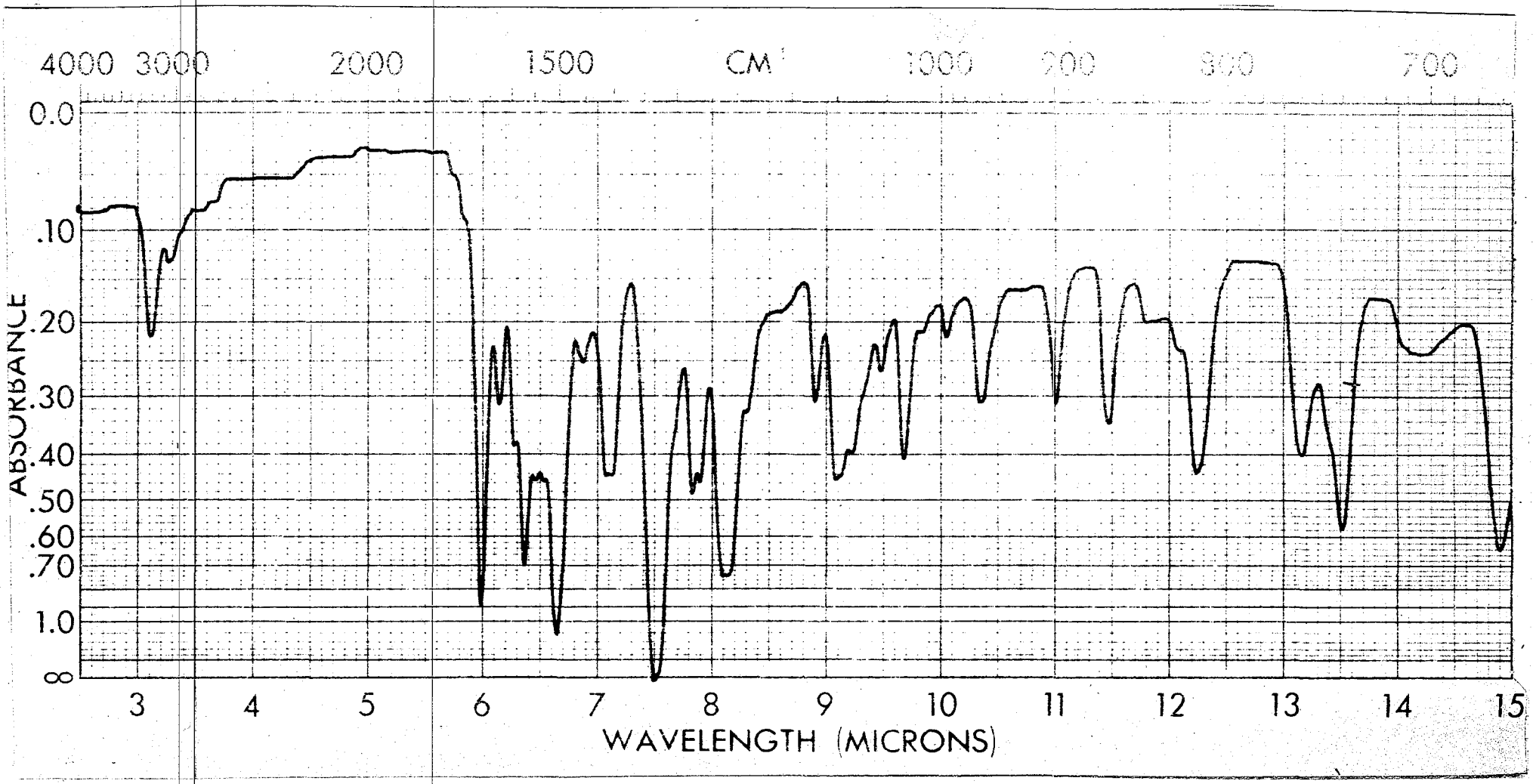


PYRROLE-2-AL(2', 4' DIHYDROXY) ACETOPHENONE



PYRROLE-2-AL(3'-NITRO) ACETOPHENONE

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